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=> s cancer or carcinoma or sarcoma or tumor or malignant or leukemia or lymphoma
   4 FILES SEARCHED...
L1     5184193 CANCER OR CARCINOMA OR SARCOMA OR TUMOR OR MALIGNANT OR LEUKEMIA
               OR LYMPHOMA

=> s (DNA methylation) (p) inhibitor
L2        1777 (DNA METHYLATION) (P) INHIBITOR

=> s cytidine or decitabine
L3       32691 CYTIDINE OR DECITABINE

=> s l2 or l3
L4       34371 L2 OR L3

=> s (histone deacetylase) (p) inhibitor
L5        3671 (HISTONE DEACETYLASE) (P) INHIBITOR

=> s (hydroxamic acid) or (trichostatin A) or oxamflatin or pyroxamide or (m-carboxy cinnamic acid
   4 FILES SEARCHED...
L6       16304 (HYDROXAMIC ACID) OR (TRICHOSTATIN A) OR OXAMFLATIN OR PYROXAMID
               E OR (M-CARBOXY CINNAMIC ACID) OR (BISHYDROXAMIC ACID)

=> s (trapoxin A) or apicidin or depsipeptide or fr901228
L7        4070 (TRAPOXIN A) OR APICIDIN OR DEPSIPEPTIDE OR FR901228

=> s benzamide or MS-27-275
L8       27241 BENZAMIDE OR MS-27-275

=> s butyrate or (butyric acid) or phenylutyrate or (arginine butyrate) or depudecin
L9      105163 BUTYRATE OR (BUTYRIC ACID) OR PHENYLUTYRATE OR (ARGININE BUTYRAT
               E) OR DEPUDECIN

=> s l5 or l6 or l7 or l8 or l9
L10     152314 L5 OR L6 OR L7 OR L8 OR L9

=> d his

     (FILE 'HOME' ENTERED AT 19:31:41 ON 21 NOV 2002)

     FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH, AGRICOLA' ENTERED AT
     19:32:09 ON 21 NOV 2002
L1      5184193 S CANCER OR CARCINOMA OR SARCOMA OR TUMOR OR MALIGNANT OR LEUKE
L2         1777 S (DNA METHYLATION) (P) INHIBITOR
L3        32691 S CYTIDINE OR DECITABINE
L4        34371 S L2 OR L3
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L5          3671 S (HISTONE DEACETYLASE) (P) INHIBITOR
L6         16304 S (HYDROXAMIC ACID) OR (TRICHOSTATIN A) OR OXAMFLATIN OR PYROXA
L7          4070 S (TRAPOXIN A) OR APICIDIN OR DEPSIPEPTIDE OR FR901228
L8         27241 S BENZAMIDE OR MS-27-275
L9        105163 S BUTYRATE OR (BUTYRIC ACID) OR PHENYLUTYRATE OR (ARGININE BUTY
L10       152314 S L5 OR L6 OR L7 OR L8 OR L9

=> s l1 (p) l4 (p) l10
L11         155 L1 (P) L4 (P) L10

=> s l11 (p) treat?
L12          95 L11 (P) TREAT?

=> duplicate remove l12
DUPLICATE PREFERENCE IS 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH'
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PROCESSING COMPLETED FOR L12
L13           27 DUPLICATE REMOVE L12 (68 DUPLICATES REMOVED)

=> d l13 1-27 ibib abs

L13  ANSWER 1 OF 27  CAPLUS  COPYRIGHT 2002 ACS
ACCESSION NUMBER:         2002:832643  CAPLUS
DOCUMENT NUMBER:          137:304765
TITLE:                    Compositions and methods for reestablishing gene
                          transcription through inhibition of DNA methylation
                          and histone deacetylase
INVENTOR(S):              Dimartino, Jorge
PATENT ASSIGNEE(S):       Supergen, Inc., USA
SOURCE:                   PCT Int. Appl., 54 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.        KIND  DATE           APPLICATION NO.  DATE
     ---------------   ----  --------       ---------------  --------
     WO 2002085400      A1   20021031       WO 2002-US12092  20020419
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
             CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
             GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
             LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
             PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ,
             UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU,
             TJ, TM
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH,
             CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR,
             BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
PRIORITY APPLN. INFO.:                  US 2001-841744   A1 20010424
AB   Compns. and methods are provided for ***treating*** diseases assocd.
     with aberrant silencing of gene expression such as ***cancer*** by
     reestablishing the gene expression through inhibition of DNA
     hypomethylation and ***histone*** ***deacetylase*** . The method
     comprises: administering to a patient suffering from the disease a
     therapeutically effective amt. of a ***DNA*** ***methylation***
     ***inhibitor*** such as a cysteine analog such as ***decitabine*** ,
     in combination with an effective amt. of ***histone***
     ***deacetylase*** ***inhibitor*** such as ***hydroxamic***
     ***acid*** , cyclic peptide, ***benzamide*** , ***butyrate*** , and
     ***depudecin*** .
REFERENCE COUNT:          5     THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS
                                RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13  ANSWER 2 OF 27     MEDLINE                          DUPLICATE 1
ACCESSION NUMBER:   2002241174     MEDLINE
DOCUMENT NUMBER:    21975197   PubMed ID: 11850427
TITLE:              Maintenance of integrated proviral gene expression requires
                    Brm, a catalytic subunit of SWI/SNF complex.
AUTHOR:             Mizutani Taketoshi; Ito Taiji; Nishina Mitsue; Yamamichi
                    Nobutake; Watanabe Akiko; Iba Hideo
CORPORATE SOURCE:   Division of Host-Parasite Interaction, Department of
```

Microbiology and Immunology, Institute of Medical Science, University of Tokyo, 4-6-1 Shirokanedai, Minato-ku, Tokyo 108-8639, Japan.
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (2002 May 3) 277 (18) 15859-64.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200207
ENTRY DATE: Entered STN: 20020430
Last Updated on STN: 20020703
Entered Medline: 20020702

AB We show here that murine ***leukemia*** virus-based retrovirus vector transgene expression is rapidly silenced in human ***tumor*** cell lines lacking expression of Brm, a catalytic subunit of the SWI/SNF chromatin remodeling complex, even though these vectors can successfully enter, integrate, and initiate transcription. We detected this gene silencing as a reduction in the ratio of cells expressing the exogenous gene rather than a reduction in the average expression levels, indicating that down-regulation occurs in an all-or-none manner. Retroviral gene expression was protected from silencing and maintained in Brm-deficient host cells by exogenous expression of Brm but not BRG1, an alternative ATPase subunit in the SWI/SNF complex. Introduction of exogenous Brm to these cells suppressed recruitment of protein complexes containing YY1 and ***histone*** ***deacetylase*** (HDAC) 1 and 2 to the 5'-long terminal repeat region of the integrated provirus, leading to the enhancement of acetylation of specific lysine residues in histone H4 located in this region. Consistent with these observations, ***treatment*** of Brm-deficient cells with HDAC ***inhibitors*** but not ***DNA*** ***methylation*** ***inhibitors*** suppressed retroviral gene silencing. These results suggest that the Brm-containing SWI/SNF complex subfamily (trithorax-G) and a complex including YY1 and HDACs (Polycomb-G) counteract each other to maintain transcription of exogenously introduced genes.

L13 ANSWER 3 OF 27 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 2002628935 IN-PROCESS
DOCUMENT NUMBER: 22274615 PubMed ID: 12386812
TITLE: gamma-Catenin expression is reduced or absent in a subset of human lung cancers and re-expression inhibits transformed cell growth.
AUTHOR: Winn Robert A; Bremnes Roy M; Bemis Lynne; Franklin Wilbur A; Miller York E; Cool Carlyne; Heasley Lynn E
CORPORATE SOURCE: Veterans Administration Medical Center, Denver, Colorado, CO 80220, USA, and Department of Medicine, University of Colorado Health Sciences Center, Denver, Colorado, CO 80262, USA.
SOURCE: ONCOGENE, (2002 Oct 24) 21 (49) 7497-506.
Journal code: 8711562. ISSN: 0950-9232.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20021019
Last Updated on STN: 20021019

AB Lung ***cancer*** is a heterogeneous disease categorized into multiple subtypes of ***cancers*** which likely arise from distinct patterns of genetic alterations and disruptions. Precedent exists for a role of beta-catenin, a downstream component of the Wnt signaling pathway that serves as a transcriptional co-activator with TCF/LEF, in several human ***cancers*** including colon ***carcinomas*** . In this study, we observed that beta-catenin was highly and uniformly expressed in a panel of NSCLC cell lines and primary lung ***tumors*** . By contrast, gamma-catenin was weakly expressed or absent in several NSCLC cell lines and immunohistochemical analysis of primary NSCLC ***tumors*** revealed negligible to weak gamma-catenin staining in approximately 30% of the specimens. ***Treatment*** of NSCLC cells expressing reduced gamma-catenin protein with 5-aza-2'-deoxycytidine (5aza2dc), a ***DNA*** ***methylation*** ***inhibitor*** , or ***trichostatin*** ***A*** (TSA), a ***histone*** ***deacetylase***

inhibitor , increased gamma-catenin protein content in NSCLC cells with low gamma-catenin expression. Significantly, the activity of a beta-catenin/TCF-dependent luciferase reporter was markedly elevated in the NSCLC cell lines that underexpressed gamma-catenin relative to those lines that highly expressed gamma-catenin. Moreover, transfection of these cells with a gamma-catenin expression plasmid reduced the elevated TCF activity by 85% and strongly inhibited cell growth on tissue culture plastic as well as anchorage-independent growth in soft agar. This study shows that gamma-catenin can function as an ***inhibitor*** of beta-catenin/TCF-dependent gene transcription and highlights gamma-catenin as a potentially novel ***tumor*** suppressor protein in a subset of human NSCLC ***cancers*** . doi:10.1038/sj.onc.1205963

L13 ANSWER 4 OF 27 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 2002404779 MEDLINE
DOCUMENT NUMBER: 22149195 PubMed ID: 12154410
TITLE: Reactivating the expression of methylation silenced genes in human cancer.
AUTHOR: Karpf Adam R; Jones David A
CORPORATE SOURCE: Huntsman Cancer Institute, University of Utah, 2000 Circle of Hope, Salt Lake City, Utah, UT 84112, USA.. adam.karpf@hci.utah.edu
CONTRACT NUMBER: P01-CA73992 (NCI)
SOURCE: ONCOGENE, (2002 Aug 12) 21 (35) 5496-503. Ref: 67
Journal code: 8711562. ISSN: 0950-9232.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200208
ENTRY DATE: Entered STN: 20020803
Last Updated on STN: 20020823
Entered Medline: 20020822
AB ***DNA*** ***methylation*** alterations are now widely recognized as a contributing factor in human tumorigenesis. A significant number of ***tumor*** suppressor genes are transcriptionally silenced by promoter hypermethylation, and recent research implicates alterations in chromatin structure as the mechanistic basis for this repression. The enzymes responsible for catalyzing DNA-cytosine methylation, as well as the proteins involved in interpreting the ***DNA*** ***methylation*** signal, have now been elucidated. Technological advances, including gene expression microarrays and genome scanning techniques, have allowed the comprehensive measurement of ***DNA*** ***methylation*** changes in human ***cancers*** . An important distinction between ***DNA*** ***methylation*** (epigenetic) and mutation or deletion (genetic) ***tumor*** suppressor gene inactivation is that epigenetic inactivation can be abrogated by small molecules, including DNA methyltransferase and ***histone*** ***deacetylase*** ***inhibitors*** . Further, strategies have been developed that combine ***treatments*** with drugs that reactivate silenced gene expression with secondary agents that target the re-expressed genes and/or reconstituted signal transduction pathways. In this review, we will discuss in detail the mechanisms of gene silencing by ***DNA*** ***methylation*** , the techniques used to decipher the complement of methylation-inactivated genes in human ***cancers*** , and current and future strategies for reactivating the expression of methylation-silenced genes.

L13 ANSWER 5 OF 27 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 2002134134 MEDLINE
DOCUMENT NUMBER: 21853694 PubMed ID: 11865062
TITLE: Precipitous release of methyl-CpG binding protein 2 and histone deacetylase 1 from the methylated human multidrug resistance gene (MDR1) on activation.
AUTHOR: El-Osta Assam; Kantharidis Phillip; Zalcberg John R; Wolffe Alan P
CORPORATE SOURCE: Sir Donald & Lady Trescowthick Research Laboratories, Peter MacCallum Cancer Institute, St. Andrews Place, East Melbourne, Victoria 3002, Australia.. s.el-osta@pmci.unimelb.edu.au
SOURCE: MOLECULAR AND CELLULAR BIOLOGY, (2002 Mar) 22 (6) 1844-57.

Journal code: 8109087. ISSN: 0270-7306.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200203
ENTRY DATE: Entered STN: 20020301
Last Updated on STN: 20020313
Entered Medline: 20020312

AB Overexpression of the human multidrug resistance gene 1 (MDR1) is a negative prognostic factor in ***leukemia*** . Despite intense efforts to characterize the gene at the molecular level, little is known about the genetic events that switch on gene expression in P-glycoprotein-negative cells. Recent studies have shown that the transcriptional competence of MDR1 is often closely associated with ***DNA*** ***methylation*** . Chromatin remodeling and modification targeted by the recognition of methylated DNA provide a dominant mechanism for transcriptional repression. Consistent with this epigenetic model, interference with DNA methyltransferase and ***histone*** ***deacetylase*** activity alone or in combination can reactivate silent genes. In the present study, we used chromatin immunoprecipitation to monitor the molecular events involved in the activation and repression of MDR1. ***Inhibitors*** of DNA methyltransferase (5-azacytidine [5aC]) and ***histone*** ***deacetylase*** (***trichostatin*** ***A*** [TSA]) were used to examine gene transcription, promoter methylation status, and the chromatin determinants associated with the MDR1 promoter. We have established that methyl-CpG binding protein 2 (MeCP2) is involved in methylation-dependent silencing of human MDR1 in cells that lack the known transcriptional repressors MBD2 and MBD3. In the repressed state the MDR1 promoter is methylated and assembled into chromatin enriched with MeCP2 and deacetylated histone. TSA induced significant acetylation of histones H3 and H4 but did not activate transcription. 5aC induced DNA demethylation, leading to the release of MeCP2, promoter acetylation, and partial relief of repression. MDR1 expression was significantly increased following combined 5aC and TSA ***treatments*** . Inhibition of ***histone*** ***deacetylase*** is not an overriding mechanism in the reactivation of methylated MDR1. Our results provide us with a clearer understanding of the molecular mechanism necessary for repression of MDR1.

L13 ANSWER 6 OF 27 MEDLINE DUPLICATE 5
ACCESSION NUMBER: 2002462208 IN-PROCESS
DOCUMENT NUMBER: 22209618 PubMed ID: 12220350
TITLE: DNA methylation: an epigenetic pathway to cancer and a promising target for anticancer therapy.
AUTHOR: Worm Jesper; Guldberg Per
CORPORATE SOURCE: Institute of Cancer Biology, Danish Cancer Society, Strandboulevarden 49, DK-2100 Copenhagen, Denmark.
SOURCE: JOURNAL OF ORAL PATHOLOGY AND MEDICINE, (2002 Sep) 31 (8) 443-9.
Journal code: 8911934. ISSN: 0904-2512.
PUB. COUNTRY: Denmark
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: IN-PROCESS; NONINDEXED; Dental Journals; Priority Journals
ENTRY DATE: Entered STN: 20020911
Last Updated on STN: 20020911

AB The unique properties of a ***cancer*** cell are acquired through a stepwise accumulation of heritable changes in the information content of proto-oncogenes and ***tumor*** suppressor genes. While gain, loss, and mutation of genetic information have long been known to contribute to tumorigenesis, it has been increasingly recognized over the past 5 years that 'epigenetic' mechanisms may play an equally important role. The main epigenetic modification of the human genome is methylation of cytosine residues within the context of the CpG dinucleotide. De novo methylation of 'CpG islands' in the promoter regions of ***tumor*** suppressor genes may lead to transcriptional silencing through a complex process involving histone deacetylation and chromatin condensation, and thus represents a tumorigenic event that is functionally equivalent to genetic changes like mutation and deletion. ***DNA*** ***methylation*** is interesting from a diagnostic viewpoint because it may be easily detected in DNA released from neoplastic and preneoplastic lesions into serum, urine or sputum, and from a therapeutic viewpoint because epigenetically

silenced genes may be reactivated by ***inhibitors*** of ***DNA*** ***methylation*** and/or ***histone*** ***deacetylase*** . A better understanding of epigenetic mechanisms leading to ***tumor*** formation and chemoresistance may eventually improve current ***cancer*** ***treatment*** regimens and be instructive for a more rational use of anticancer agents.

L13 ANSWER 7 OF 27 MEDLINE DUPLICATE 6
ACCESSION NUMBER: 2002287775 MEDLINE
DOCUMENT NUMBER: 22022229 PubMed ID: 11987150
TITLE: Silencing of pi-class glutathione S-transferase in MDA PCa 2a and MDA PCa 2b cells.
AUTHOR: Vidanes Genevieve M; Paton Vince; Wallen Eric; Peehl Donna M; Navone Nora; Brooks James D
CORPORATE SOURCE: Department of Urology, Stanford University Medical Center, Pasteur Drive, Stanford, California 94305-5118, USA.
SOURCE: PROSTATE, (2002 Jun 1) 51 (4) 225-30.
Journal code: 8101368. ISSN: 0270-4137.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200206
ENTRY DATE: Entered STN: 20020528
Last Updated on STN: 20020620
Entered Medline: 20020619

AB BACKGROUND: Loss of expression of the glutathione S-transferase-pi (GSTP1) is the most common genetic alteration described in human prostate ***cancer*** , occurring in virtually all ***tumors*** regardless of grade or stage. Of the available human prostate ***cancer*** cell lines, only LNCaP mirrors this phenotype. We investigated whether the prostate ***cancer*** cell lines MDA PCa 2a and MDA PCa 2b share this phenotype. METHODS: GSTP1 protein and mRNA levels were assessed in the MDA PCa 2a and MDA PCa 2b cell lines by Western and Northern blot. ***DNA*** ***methylation*** was evaluated by Southern blot analysis of genomic DNA digested with the methylation-sensitive restriction enzymes BssHII, NotI, and SacII. Re-expression of GSTP1 was determined by RT-PCR following ***treatment*** with 5-azacytidine, a DNA methyltransferase ***inhibitor*** , and/or the ***histone*** ***deacetylase*** ***inhibitor*** ***trichostatin*** ***A*** (TSA). RESULTS: Like all human prostatic ***carcinomas*** in vivo, both the MDA PCa 2a and 2b cell lines lack protein and mRNA expression of GSTP1. This lack of expression is associated with methylation in the GSTP1 gene promoter. ***Treatment*** with the methyltransferase ***inhibitor*** 5-azacytidine resulted in re-expression of GSTP1. By itself, TSA did not result in re-expression of GSTP1, nor did it augment expression induced by 5-azacytidine. CONCLUSIONS: MDA PCa 2a and 2b appear to be useful models of human prostatic ***carcinoma*** in that they lack expression of GSTP1 due to gene silencing via promoter methylation. Inhibition of histone acetylation does not appear to affect GSTP1 expression.

L13 ANSWER 8 OF 27 MEDLINE DUPLICATE 7
ACCESSION NUMBER: 2002461697 MEDLINE
DOCUMENT NUMBER: 22209015 PubMed ID: 12220518
TITLE: Hypermethylation and histone deacetylation lead to silencing of the maspin gene in human breast cancer.
AUTHOR: Maass Nicolai; Biallek Marco; Rosel Frank; Schem Christian; Ohike Nobuyuki; Zhang Ming; Jonat Walter; Nagasaki Koichi
CORPORATE SOURCE: Department of Obstetrics and Gynecology, Division of Gynecologic Oncology, University of Kiel, Michaelisstrasse 16, 24105 Kiel, Germany.
SOURCE: BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (2002 Sep 13) 297 (1) 125-8.
Journal code: 0372516. ISSN: 0006-291X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200210
ENTRY DATE: Entered STN: 20020911
Last Updated on STN: 20021030

Entered Medline: 20021029

AB Maspin is a member of the [redacted]ine protease ***inhibitor*** [redacted]family with ***tumor*** suppressing activity in breast ***cancer*** . Maspin expression was found in normal breast epithelial cells, but was frequently decreased in breast ***cancer*** cells and lost in metastatic cells. In this study, we examined the regulatory mechanism of maspin expression and described the re-activation of maspin expression in a series of maspin-negative breast ***cancer*** cell lines. All of the 6 maspin-negative breast ***cancer*** cells showed induction of maspin promoter activity in a promoter reporter assay. In addition, the ***treatment*** of 5-aza-2(') deoxycytidine, ***trichostatin*** ***A*** or a combination of both led to the re-expression of maspin in a series of maspin-negative breast ***cancer*** cell lines. These findings indicate that ***DNA*** ***methylation*** and/or histone deacetylation are/is partially responsible for the silencing of maspin gene expression in breast ***cancer*** cells. The re-expression of maspin by pharmacological intervention potentially offers a promising new target as a therapeutic option in breast ***cancer*** .

L13 ANSWER 9 OF 27 MEDLINE DUPLICATE 8
ACCESSION NUMBER: 2002000145 MEDLINE
DOCUMENT NUMBER: 21624913 PubMed ID: 11753657
TITLE: Increased expression of unmethylated CDKN2D by 5-aza-2'-deoxycytidine in human lung cancer cells.
AUTHOR: Zhu W G; Dai Z; Ding H; Srinivasan K; Hall J; Duan W; Villalona-Calero M A; Plass C; Otterson G A
CORPORATE SOURCE: Division of Hematology/Oncology, Department of Internal Medicine, The Ohio State University-Comprehensive Cancer Center, Columbus, OH 43210, USA.
CONTRACT NUMBER: P30 CA16058 (NCI)
SOURCE: ONCOGENE, (2001 Nov 22) 20 (53) 7787-96.
Journal code: 8711562. ISSN: 0950-9232.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200201
ENTRY DATE: Entered STN: 20020102
Last Updated on STN: 20020125
Entered Medline: 20020110

AB DNA hypermethylation of CpG islands in the promoter region of genes is associated with transcriptional silencing. ***Treatment*** with hypo-methylating agents can lead to expression of these silenced genes. However, whether inhibition of ***DNA*** ***methylation*** influences the expression of unmethylated genes has not been extensively studied. We analysed the methylation status of CDKN2A and CDKN2D in human lung ***cancer*** cell lines and demonstrated that the CDKN2A CpG island is methylated, whereas CDKN2D is unmethylated. ***Treatment*** of cells with 5-aza-2'-deoxycytidine (5-Aza-CdR), an ***inhibitor*** of DNA methyltransferase 1, induced a dose and duration dependent increased expression of both p16(INK4a) and p19(INK4d), the products of CDKN2A and CDKN2D, respectively. These data indicate that global DNA demethylation not only influences the expression of methylated genes but also of unmethylated genes. Histone acetylation is linked to methylation induced transcriptional silencing. ***Depsipeptide*** , an ***inhibitor*** of ***histone*** ***deacetylase*** , acts synergistically with 5-Aza-CdR in inducing expression of p16(INK4a) and p19(INK4d). However, when cells were ***treated*** with higher concentrations of 5-Aza-CdR and ***depsipeptide*** , p16(INK4a) expression was decreased together with significant suppression of cell growth. Interestingly, p19(INK4d) expression was enhanced even more by the higher concentrations of 5-Aza-CdR and ***depsipeptide*** . Our data suggest that p19(INK4d) plays a distinct role from other INK4 family members in response to the cytotoxicity induced by inhibition of ***DNA*** ***methylation*** and histone deacetylation.

L13 ANSWER 10 OF 27 MEDLINE DUPLICATE 9
ACCESSION NUMBER: 2001231597 MEDLINE
DOCUMENT NUMBER: 21221066 PubMed ID: 11309512
TITLE: Selective association of the methyl-CpG binding protein MBD2 with the silent p14/p16 locus in human neoplasia.
AUTHOR: Magdinier F; Wolffe A P

CORPORATE SOURCE: Laboratory of Molecular Embryology, National Institute of Child Health and Human Development, National Institutes of Health, Building 18T, Room 106, Bethesda, MD 20892, USA.. FrederiqueM@intra.niddk.nih.gov
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (2001 Apr 24) 98 (9) 4990-5. Journal code: 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200105
ENTRY DATE: Entered STN: 20010529
Last Updated on STN: 20010529
Entered Medline: 20010521

AB ***DNA*** ***methylation*** of ***tumor*** suppressor genes is a common feature of human ***cancer*** . The cyclin-dependent kinase ***inhibitor*** gene p16/Ink4A is hypermethylated in a wide range of ***malignant*** tissues and the p14/ARF gene located 20 kb upstream on chromosome 9p21 is also methylated in ***carcinomas*** . p14/ARF (ARF, alternative reading frame) does not inhibit the activities of cyclins or cyclin-dependent kinase complexes; however, the importance of the two gene products in the etiology of ***cancer*** resides in their involvement in two major cell cycle regulatory pathways: p53 and the retinoblastoma protein, Rb, respectively. Distinct first exons driven from separate promoters are spliced onto the common exons 2 and 3 and the resulting proteins are translated in different reading frames. Both genes are expressed in normal cells but can be alternatively or coordinately silenced when their CpG islands are hypermethylated. Herein, we examined the presence of methyl-CpG binding proteins associated with aberrantly methylated promoters, the distribution of acetylated histones H3 and H4 by chromatin immunoprecipitation assays, and the effect of chemical ***treatment*** with 5-aza-2'-deoxycytidine (5aza-dC) and ***trichostatin*** ***A*** on gene induction in colon cell lines by quantitative reverse transcriptase-PCR. We observed that the methyl-CpG binding protein MBD2 is targeted to methylated regulatory regions and excludes the acetylated histones H3 and H4, resulting in a localized inactive chromatin configuration. When methylated, the genes can be induced by 5aza-dC but the combined action of 5aza-dC and ***trichostatin*** ***A*** results in robust gene expression. Thus, methyl-CpG binding proteins and ***histone*** ***deacetylases*** appear to cooperate in vivo, with a dominant effect of ***DNA*** ***methylation*** toward histone acetylation, and repress expression of ***tumor*** suppressor genes hypermethylated in ***cancers*** .

L13 ANSWER 11 OF 27 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:258571 BIOSIS
DOCUMENT NUMBER: PREV200100258571
TITLE: Induction of HTLV-1 tax and immune genes in infected cells by histone deacetylase inhibition and DNA demethylation agents.
AUTHOR(S): Villanueva, Raul (1); Sanin, Luis; Arturo, Alvaro; Choles, Franklin; Dangond, Fernando
CORPORATE SOURCE: (1) Brigham and Women's Hospital, 77 Avenue Louis Pasteur, Him., Boston, MA, 02115 USA
SOURCE: FASEB Journal, (March 8, 2001) Vol. 15, No. 5, pp. A1230. print.
Meeting Info.: Annual Meeting of the Federation of American Societies for Experimental Biology on Experimental Biology 2001 Orlando, Florida, USA March 31-April 04, 2001
ISSN: 0892-6638.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

AB HTLV-1 is a retrovirus associated with adult T cell ***leukemia*** / ***lymphoma*** (ATLL) and with the human disease HTLV-1 associated myelopathy/tropical spastic paraparesis (HAM/TSP). We sought to determine whether agents that block histone deacetylation or ***DNA*** ***methylation*** could influence the expression of host and viral genes in HTLV-1 infected immune cells. We blocked ***histone*** ***deacetylases*** (HDACs) and ***DNA*** ***methylation*** with ***Trichostatin*** ***A*** and 5-Azacytidine, respectively. We found

that both ***treatments*** led to upregulation of HTLV-1 Tax and of several immune-related mRNA including genes with immune suppressor function but also genes involved in tissue infiltration. Our findings have important implications for our understanding of viral and immune gene regulation and for the use of HDAC ***inhibitors*** in the ***treatment*** of viral-induced autoimmunity and ***cancer*** .

L13 ANSWER 12 OF 27 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2002:261622 BIOSIS
DOCUMENT NUMBER: PREV200200261622
TITLE: Preclinical evaluation of the efficacy of STI571 in combination with a variety of novel anticancer agents.
AUTHOR(S): La Rosee, Paul (1); Johnson, Kara (1); Moseson, Erika M. (1); O'Dwyer, Michael (1); Druker, Brian J. (1)
CORPORATE SOURCE: (1) Division Hematology and Medical Oncology, Oregon Health and Science University, Portland, OR USA
SOURCE: Blood, (November 16, 2001) Vol. 98, No. 11 Part 1, pp. 839a. http://www.bloodjournal.org/. print.
Meeting Info.: 43rd Annual Meeting of the American Society of Hematology, Part 1 Orlando, Florida, USA December 07-11, 2001
ISSN: 0006-4971.
DOCUMENT TYPE: Conference
LANGUAGE: English
AB STI571, a Bcr-Abl tyrosine kinase ***inhibitor*** has significant clinical activity in all phases of CML. Although durable responses have been seen in chronic phase patients, not all chronic phase patients achieve a cytogenetic response. Further, resistance or relapse during ***treatment*** with single agent STI571 have been observed in the majority of blast crisis patients. To determine whether the activity of STI571 could be enhanced, combinations of STI571 with other anti-leukemic agents were evaluated for activity against Bcr-Abl positive cell lines and in colony forming assays in vitro. We evaluated the cytotoxicity of arsenic trioxide (As2O3, Trisenox) and the chromatin modifiers 5-Aza-2-deoxycytidine (***decitabine***) and ***Trichostatin*** - ***A*** alone and in combination with STI571 against Bcr-Abl positive and negative cell lines and primary CML cells derived from chronic phase patients prior to ***treatment*** with STI571. As with other chemotherapeutic agents, significantly higher concentrations of As2O3 were required to achieve a 50% growth inhibition (IC50) of Bcr-Abl positive cell lines, K562 (1.11 muM+-0.075) and MO7p210 (1.99 muM+-0.22) than those required to inhibit the growth of Bcr-Abl negative cells, MO7e (0.81 muM+-0.18) and 32D (0.52 muM+-0.18). These levels of As2O3 are within a clinically achievable range. Cotreatment of K562 and MO7p210 cells with approximately equipotent doses of As2O3 and STI571 additively inhibits proliferation in a growth inhibition range up to 80%. Data analysis by the median-effect method (Chou & Talalay), which calculates the combination-index (CI) at different levels of inhibition, suggests that at >80% levels of inhibition, moderate synergy might be achievable. In colony forming assays using CML patient samples, combination ***treatment*** showed increased antiproliferative effects as compared with STI571 alone. Combinations of 0.1 or 0.25 muM STI571 with 0.4 or 0.8muM As2O3 (CFU-GM) and 0.8muM As2O3 (BFU-E) were significantly more potent in inhibiting colony formation as compared to ***treatment*** with STI571 alone. ***Decitabine*** is a hypomethylating agent that has activity in the ***treatment*** of CML blast crisis but has a narrow therapeutic window due to hematological toxicity. In MTT-assays with K562 cells, the combination of ***decitabine*** with STI571 revealed synergistic activity as seen by CI-values <1 at the IC50 (CI=0.6+-0.24) and IC75 (CI=0.6+-0.08) doses. This synergistic potential was also seen in MO7p210 cells (IC50: CI=0.81+-0.07 and IC75: CI=0.69+-0.1). Colony forming assays assessing the effects of ***decitabine*** on primary CML cells are ongoing. The triple combination of ***Trichostatin*** - ***A*** , a ***histone*** ***deacetylase*** ***inhibitor*** , ***decitabine*** and STI571 indicate antagonism (CI>1), which is in contrast to findings in non-leukemic ***malignant*** cell lines, where the combination of ***Trichostatin*** - ***A*** and ***decitabine*** led to enhanced apoptosis compared to single agent ***treatment*** . Experiments are ongoing with combination of ***Trichostatin*** - ***A*** and STI571 and ***Trichostatin*** - ***A*** with ***decitabine*** to determine which of these combinations accounts for this antagonism. These data suggest that

combinations of STI571 with As2O3 or ***decitabine*** might be considered as therapeutic alternatives that could circumvent resistance to STI571, particularly in patients with advanced disease.

L13 ANSWER 13 OF 27 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2002:241192 BIOSIS
DOCUMENT NUMBER: PREV200200241192
TITLE: Transcription modulation: A pilot study of sodium phenylbutyrate plus 5-azacytidine.
AUTHOR(S): Camacho, L. H. (1); Ryan, J.; Chanel, S. (1); Maslak, P. (1); Salomoni, P.; Jakubowski, A. (1); Klimek, V. (1); Camastra, D. (1); Nimer, S. (1); Pandolfi, P. P.; Soignet, S. L. (1)
CORPORATE SOURCE: (1) Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY USA
SOURCE: Blood, (November 16, 2001) Vol. 98, No. 11 Part 1, pp. 460a. http://www.bloodjournal.org/. print.
Meeting Info.: 43rd Annual Meeting of the American Society of Hematology, Part 1 Orlando, Florida, USA December 07-11, 2001
ISSN: 0006-4971.
DOCUMENT TYPE: Conference
LANGUAGE: English
AB Transcriptional silencing of ***tumor*** suppressor genes occurs in ***cancer*** cell by ***DNA*** ***methylation*** and by histone deacetylation (HDAC). Recently, novel agents that target these mechanisms have been developed. To evaluate the role of transcription modulation as a form of anticancer therapy, we initiated a clinical study with 5-azacytidine (5-AC) plus sodium phenylbutyrate (PB), ***inhibitors*** of methyltransferase and ***histone*** ***deacetylase*** , respectively. ***Treatment*** scheme entailed subcutaneous injections of 5-AC for 7 consecutive days (75 mg/m2/day) followed by 5 days of intravenous doses of PB (200 mg/kg/day), repeated on a 21 to 28 day schedule contingent on tolerability and response. To date, 6 pts with myelodysplasia/secondary AML have received at least one cycle of therapy (range, 1-3). Reduction in bone marrow blast count as well as increased percent of myeloid maturation was observed in 4 pts; one pt with relapsed ***leukemia*** post BMT that had a complete elimination of bone marrow blasts after one cycle of therapy, and subsequently underwent a second alloBMT. Peripheral blood samples and bone marrow were collected before 5-AC, on day 8 (at completion of 5-AC, and before beginning PB), and at the completion of PB, and an increase in histone acetylation was consistently detected in peripheral blood and bone marrow samples post PB. Selected genes commonly silenced (eg. p15INK4b in myelogenous ***leukemia***) are being analyzed for alteration in methylation and expression, and alterations in methylation of the p15INK4b (CDKN2b) promoter, a region commonly hypermethylated and associated with transcriptional silencing, is being assessed using real time PCR. ***Treatment*** has been relatively well tolerated; adverse reactions associated with 5-AC include fatigue, nausea, vomiting, and local tenderness at injection sites. PB was associated with transient somnolence and drowsiness. This ongoing study will evaluate the effects of these agents upon gene methylation and histone deacetylation in target genes, and the safety and potential antitumor effects of this combination.

L13 ANSWER 14 OF 27 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2002:129878 BIOSIS
DOCUMENT NUMBER: PREV200200129878
TITLE: Reactivation of a silenced, methylated p16INK4a gene by low-dose 5-aza-2'-deoxycytidine requires activation of the p38 map kinase signal transduction pathway.
AUTHOR(S): Lavelle, Donald (1); DeSimone, Joseph; Hankewych, Maria; Kousnetzova, Tatiana; Chen, Yi-Hsiang
CORPORATE SOURCE: (1) Department of Medicine, University of Illinois at Chicago, Chicago, IL USA
SOURCE: Blood, (November 16, 2001) Vol. 98, No. 11 Part 1, pp. 105a. http://www.bloodjournal.org/. print.
Meeting Info.: 43rd Annual Meeting of the American Society of Hematology, Part 1 Orlando, Florida, USA December 07-11, 2001
ISSN: 0006-4971.
DOCUMENT TYPE: Conference

LANGUAGE: English

AB ***DNA*** ***methylation*** silences the expression of multiple ***tumor*** supressor genes in many types of ***tumors*** by inducing repressive chromatin structures mediated by binding of methylated DNA binding (MBD) proteins associated with protein complexes containing ***histone*** ***deacetylase*** (HDAC) activity and chromatin remodeling factors. ***Treatment*** with the DNA demethylating drug 5-aza-2'-deoxycytidine (***decitabine*** ; DAC) reactivates the expression of silenced, methylated ***tumor*** suppressor genes by alleviating methylation-mediated repression. The synergistic reactivation of silenced, methylated genes by a combination of the HDAC ***inhibitor*** ***trichostatin*** ***A*** with low doses of DAC inducing limited demethylation demonstrated the important role of HDAC in the maintenance of methylation-mediated gene silencing (Cameron et al, Nat Genet 21:103, 1999). Whether DAC induces other activities that may be essential in the reactivation of silenced, methylated genes has not been investigated. Environmental and pharmacologic stress activates alternative map kinase signal tranduction pathways resulting in MSK 1-mediated phosphorylation of a minute fraction of histone H3 on serine 10. Phosphorylation of H3 increases sensitivity to hyperacetylation by HDAC ***inhibitors*** and histone acetyltransferases. Our objective in these experiments was to: 1) determine whether DAC ***treatment*** activated map kinase signal transduction pathways, and 2) investigate the role of map kinase pathways in the reactivation of silenced, methylated ***tumor*** suppressor genes. We observed that DAC ***treatment*** reactivated expression of a silenced, methylated p16INK4a gene in HS-Sultan cells in a dose-dependent manner (10-7 to 10-6 M). Phosphorylation of p38 map kinase was increased in a linear, dose-dependent manner at DAC concentrations ranging from 10-8 to 10-6 M. No activation of ERK 1/2 was observed. Increased phosphorylation of p38 was observed as early as 12 hours following drug addition. The ability of DAC to reactivate p16INK4a expression was inhibited by the p38 map kinase ***inhibitor*** SB203580 (10muM) at low doses (10-7 M) but not high doses (10-6 M) of DAC. The degree of inhibition was reduced with increasing DAC dose. The ERK 1/2 ***inhibitor*** PD098059 had no effect. Neither SB203580 or PD098059 affected cell growth and therefore the inhibition of p16INK4a reactivation was not due to inhibition of DAC incorporation into DNA H89 (10muM), at a concentration shown to preferentially inhibit MSK 1 (Thomson et al, EMBO J:4779, 1999), also inhibited reactivation of p16INK4a at low doses of DAC, suggesting that MSK 1-mediated histone H3 phosphorylation was required for p16INK4a reactivation. Our results demonstrate that activation of the p38 map kinase signal transduction pathway is required for reactivation of a silenced methylated p16INK4 gene by low dose DAC and suggest that this is due to the induction of an active chromatin configuration through phosphorylation of histone H3 by MSK 1. Therefore, reactivation of a silenced, methylated p16INK4a ***tumor*** suppressor gene at low doses of DAC requires both a reduction of ***DNA*** ***methylation*** density leading to loss of repressive MBDHDAC complexes and induction of an active chromatin configuration through the p38 map kinase signal transduction pathway.

L13 ANSWER 15 OF 27 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 2002:129870 BIOSIS

DOCUMENT NUMBER: PREV200200129870

TITLE: Depsipeptide (FR901228) induces lysine-specific histone acetylation, differentiation and apoptosis in acute myeloid leukemia cells and demonstrates synergy with decitabine.

AUTHOR(S): Maghraby, Eman A. (1); Murphy, Thimoty (1); Parthun, Mark R.; Klisovic, Marko (1); Sklenar, Amy; Archer, Kellie J. (1); Whitman, Susan (1); Grever, Michael R. (1); Caligiuri, Michael A. (1); Byrd, John C. (1); Marcucci, Guido (1)

CORPORATE SOURCE: (1) Comprehensive Cancer Center, Ohio State University, Columbus, OH USA

SOURCE: Blood, (November 16, 2001) Vol. 98, No. 11 Part 1, pp. 103a-104a. http://www.bloodjournal.org/. print.
Meeting Info.: 43rd Annual Meeting of the American Society of Hematology, Part 1 Orlando, Florida, USA December 07-11, 2001
ISSN: 0006-4971.

DOCUMENT TYPE: Conference

LANGUAGE: English

AB Alterations in histone acetylation and, in turn, chromatin remodeling are important mechanisms in leukemogenesis. In t(8;21)(q22;q22) AML, the AML1/ETO fusion protein disrupts normal hematopoiesis by recruiting the transcription repressor ***histone*** ***deacetylase*** (HDAC) complex NCOR/Sin3/HDAC1 to AML1 target genes. The importance of histone acetylation to other types of AML is uncertain. We Studied the biological effects of ***depsipeptide*** (***FR901228***), a HDAC ***inhibitor*** currently in clinical trials, on both AML1/ETO-positive and negative AML cell lines and primary ***leukemia*** cells. Following 24-hour exposure of AML1/ETO-positive Kasumi-1 cell line to 0.1 to 100 nmol/L ***depsipeptide*** , increasing histone H3 and H4 acetylation levels were noted by immunoblotting analysis. These changes occurred in a specific pattern of lysine residue acetylation (i.e., more pronounced at H4 K5, 8 and 12 and less at K16). A significant ***depsipeptide*** -induced dose-dependent (0.1 to 100 nmol/L; p<0.0001) and time-dependent (4 to 96 h; p<0.0001) decrease in cell viability was found as assessed by trypan blue and annexin-V/PI staining. Similar findings relative to loss of viability and change in histone acetylation were observed in the K562 cell line and in primary ***leukemia*** cells. As ***histone*** ***deacetylase*** ***inhibitors*** have been shown to promote differentiation and enhance transcription, we examined for both processes concurrent with in vitro ***treatment*** in the Kasumi-1 cell line. Up-regulation of CD11b, a myeloid differentiation antigen, and expression of IL-3, an AML1 target gene, following exposure to depsipetide was demonstrated by flow-cytometry and RT-PCR assays, respectively. We next examined if agents that reverse methylation (ie. ***decitabine***) also increase histone acetylation and apoptosis in AML cells. These studies demonstrated that ***decitabine*** (2.5 umol/L) could enhance histone H4 acetylation at low levels of ***depsipeptide*** (1 nmol/L) ***treatment*** as compared to ***depsipeptide*** or ***decitabine*** alone. Enhanced acetylation of H4 was associated with a significantly higher 24-h apoptosis rate as compared to either agent alone. These data demonstrate that ***depsipeptide*** has significant antitumor activity in AML1/ETO-positive cells, and appears to promote transcriptional activation, differentiation, and apoptosis concurrent with increase in H3 and H4 histone acetylation. Furthermore, enhanced acetylation induced by ***decitabine*** markedly increases apoptosis. These results provide a rationale for trials with both single agent ***depsipeptide*** and those combining despipeptide with ***decitabine*** for AML ***treatment*** that target the pharmacodyamic endpoint of increasing histone acetylation in blast cells.

L13 ANSWER 16 OF 27 MEDLINE DUPLICATE 10
ACCESSION NUMBER: 2001442906 MEDLINE
DOCUMENT NUMBER: 21380725 PubMed ID: 11488527
TITLE: Antineoplastic action of 5-aza-2'-deoxycytidine and histone deacetylase inhibitor and their effect on the expression of retinoic acid receptor beta and estrogen receptor alpha genes in breast carcinoma cells.
AUTHOR: Bovenzi V; Momparler R L
CORPORATE SOURCE: Department de pharmacologie, Universite de Montreal, Quebec, Canada.
SOURCE: CANCER CHEMOTHERAPY AND PHARMACOLOGY, (2001 Jul) 48 (1) 71-6.
Journal code: 7806519. ISSN: 0344-5704.
PUB. COUNTRY: Germany: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200108
ENTRY DATE: Entered STN: 20010813
Last Updated on STN: 20010903
Entered Medline: 20010830

AB PURPOSE: During tumorigenesis several ***cancer*** -related genes can be silenced by aberrant methylation. In many cases these silenced genes can be reactivated by exposure to the ***DNA*** ***methylation*** ***inhibitor*** , 5-aza-2'-deoxycytidine (5-AZA-CdR). Histone acetylation also plays a role in the control of expression of some genes. The aim of this study was to determine the antineoplastic activities of 5-AZA-CdR and ***trichostatin*** ***A*** (TSA), either administered alone or in combination. in MDA-MB-231 breast ***carcinoma*** cells. The effects

of these drugs (alone and in combination) on the expression of the ***tumor*** suppressor gene, retinoic acid receptor (RAR beta) and of the estrogen receptor alpha gene (ER alpha), whose expression is lost in the cell line used in the study, were also investigated. METHODS: MDA-MB-231 cells were ***treated*** with 5-AZA-CdR and TSA and the antitumor activity of these drugs was determined by clonogenic assay. Total RNA was extracted from the ***treated*** cells and RT-PCR was used to determine the effect of the ***treatment*** on the expression of RAR beta and ER alpha. Methylation-sensitive PCR analysis was used to confirm that lack of expression of both genes was due to hypermethylation of their promoter regions. A single nucleotide primer extension assay was also used to quantify the reduction in ***DNA*** ***methylation*** following drug ***treatment*** . RESULTS: Both 5-AZA-CdR and TSA alone showed significant antineoplastic activity. The combination of the two drugs was synergistic with respect to MDA-MB-231 cell kill. 5-AZA-CdR alone weakly activated the expression of both RAR beta and ER alpha. TSA alone only activated RAR beta, but not ER alpha. The combination of these agents appeared to produce a greater activation of both genes. CONCLUSIONS: The interesting interaction between 5-AZA-CdR and TSA in both cell kill and ***cancer*** -related gene reactivation provides a rationale for the use of ***inhibitors*** of ***DNA*** ***methylation*** and histone deacetylation in combination for the chemotherapy of breast ***cancer*** .

L13 ANSWER 17 OF 27 MEDLINE DUPLICATE 11
ACCESSION NUMBER: 2001608502 MEDLINE
DOCUMENT NUMBER: 21539676 PubMed ID: 11683489
TITLE: Inactivation of retinoic acid receptor beta by promoter CpG hypermethylation in gastric cancer.
AUTHOR: Hayashi K; Yokozaki H; Goodison S; Oue N; Suzuki T; Lotan R; Yasui W; Tahara E
CORPORATE SOURCE: First Department of Pathology, Hiroshima University School of Medicine, Japan.. etahara@cisnet.or.jp
CONTRACT NUMBER: DE11906 (NIDCR)
p101-CA52051 (NCI)
SOURCE: DIFFERENTIATION, (2001 Aug) 68 (1) 13-21.
Journal code: 0401650. ISSN: 0301-4681.
PUB. COUNTRY: Germany: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200203
ENTRY DATE: Entered STN: 20011102
Last Updated on STN: 20020320
Entered Medline: 20020319

AB Inactivation of nuclear retinoic acid receptor beta (RARbeta) expression is implicated in tumorigenesis. We hypothesized that loss of RARbeta in gastric ***cancer*** cells may occur as a result of multiple factors, including epigenetic modifications which alter RARbeta promoter chromatin structure. We examined hypermethylation of CpG islands present in the RARbeta promoter by methylation-specific PCR and the expression of RARbeta in gastric ***cancer*** cell lines and tissues. Three (MKN-28, -45 and -74) out of eight gastric ***cancer*** cell lines had a loss of RAR expression associated with promoter methylation. RARbeta expression was retrieved in these cell lines by ***treatment*** with 5-azacytidine or by the ***histone*** ***deacetylase*** ***inhibitor*** ***trichostatin*** ***A*** . Promoter hypermethylation was detected in 64% (7/11) of gastric ***carcinoma*** tissues with reduced expression of RARbeta, whereas it was detected in 22% (2/9) of ***tumors*** with retained RARbeta expression. To investigate the functions of exogenous RARbeta in gastric ***cancer*** cells, we transfected a retroviral RARbeta expression vector (LNSbeta) into MKN-28 cells that have hypermethylation of the RARbeta promoter. Overexpression of RAR in MKN-28 cells appeared to regulate the expression of DNA methyltransferase and DNA demethylase and the acetylation of hitone H4. These results suggest that the transcriptional inactivation of the RARbeta by promoter CpG hypermethylation is frequently associated with gastric ***carcinoma*** . Our data also suggests that ***DNA*** ***methylation*** plays a pivotal role in establishing and maintaining an inactive state of RARbeta by rendering the chromatin structure inaccessible to the transcription machinery.

methylation-specific PCR analysis showed aberrant methylation of AR 5'-regulatory region in 20% of 10 primary and 28% of 14 hormone-refractory PCa samples. To clarify the effect of epigenetic regulation on AR expression, we ***treated*** three prostate ***cancer*** cell lines with a demethylating agent, 5-aza-2'-deoxycytidine (azaC), and a ***histone*** ***deacetylase*** ***inhibitor*** , ***Trichostatin*** ***A*** (TSA). In DU145, re-expression of AR mRNA was detected after ***treatment*** with azaC and/or TSA. Our results suggest that epigenetic regulations including CpG methylation and histone acetylation may play important roles in the regulation of the AR.

L13 ANSWER 20 OF 27 MEDLINE DUPLICATE 14
ACCESSION NUMBER: 2000200625 MEDLINE
DOCUMENT NUMBER: 20200625 PubMed ID: 10734315
TITLE: Evidence of epigenetic changes affecting the chromatin state of the retinoic acid receptor beta2 promoter in breast cancer cells.
AUTHOR: Sirchia S M; Ferguson A T; Sironi E; Subramanyan S; Orlandi R; Sukumar S; Sacchi N
CORPORATE SOURCE: Laboratory of Human Genetics, Hospital San Paolo, University of Milan, Milan, Italy.
SOURCE: ONCOGENE, (2000 Mar 16) 19 (12) 1556-63. Journal code: 8711562. ISSN: 0950-9232.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200004
ENTRY DATE: Entered STN: 20000505
Last Updated on STN: 20000505
Entered Medline: 20000421
AB Retinoic acid (RA)-resistance in breast ***cancer*** cells has been associated with irreversible loss of retinoic acid receptor beta, RARbeta, gene expression. Search of the causes affecting RARbeta gene activity has been oriented at identifying possible differences either at the level of one of the RARbeta promoters, RARbeta2, or at regulatory factors. We hypothesized that loss of RARbeta2 activity occurs as a result of multiple factors, including epigenetic modifications, which can pattern RARbeta2 chromatin state. Using methylation-specific PCR, we found hypermethylation at RARbeta2 in a significant proportion of both breast ***cancer*** cell lines and primary breast ***tumors*** . ***Treatment*** of cells with a methylated RARbeta2 promoter, by means of the DNA methyltransferase ***inhibitor*** 5-Aza-2'-deoxycytidine (5-Aza-CdR), led to demethylation within RARbeta2 and expression of RARbeta indicating that ***DNA*** ***methylation*** is at least one factor, contributing to RARbeta inactivity. However, identically methylated promoters can differentially respond to RA, suggesting that RARbeta2 activity may be associated to different repressive chromatin states. This supposition is supported by the finding that the more stable repressive RARbeta2 state in the RA-resistant MDA-MB-231 cell line can be alleviated by the HDAC ***inhibitor*** , ***trichostatin*** ***A*** (TSA), with restoration of RA-induced RARbeta transcription. Thus, chromatin-remodeling drugs might provide a strategy to restore RARbeta activity, and help to overcome the hurdle of RA-resistance in breast ***cancer*** .

L13 ANSWER 21 OF 27 MEDLINE DUPLICATE 15
ACCESSION NUMBER: 2000094963 MEDLINE
DOCUMENT NUMBER: 20094963 PubMed ID: 10629041
TITLE: Dynamic analysis of proviral induction and De Novo methylation: implications for a histone deacetylase-independent, methylation density-dependent mechanism of transcriptional repression.
AUTHOR: Lorincz M C; Schubeler D; Goeke S C; Walters M; Groudine M; Martin D I
CORPORATE SOURCE: Fred Hutchinson Cancer Research Center, University of Washington School of Medicine, Seattle, Washington, USA.. mlorincz@fhcrc.org
SOURCE: MOLECULAR AND CELLULAR BIOLOGY, (2000 Feb) 20 (3) 842-50. Journal code: 8109087. ISSN: 0270-7306.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200002
ENTRY DATE: Entered STN: 20000229
Last Updated on STN: 20000229
Entered Medline: 20000214

AB Methylation of cytosines in the CpG dinucleotide is generally associated with transcriptional repression in mammalian cells, and recent findings implicate histone deacetylation in methylation-mediated repression. Analyses of histone acetylation in in vitro-methylated transfected plasmids support this model; however, little is known about the relationships among de novo ***DNA*** ***methylation*** , transcriptional repression, and histone acetylation state. To examine these relationships in vivo, we have developed a novel approach that permits the isolation and expansion of cells harboring expressing or silent retroviruses. MEL cells were infected with a Moloney murine ***leukemia*** virus encoding the green fluorescent protein (GFP), and single-copy, silent proviral clones were ***treated*** weekly with the ***histone*** ***deacetylase*** ***inhibitor*** ***trichostatin*** ***A*** or the ***DNA*** ***methylation*** ***inhibitor*** 5-azacytidine. Expression was monitored concurrently by flow cytometry, allowing for repeated phenotypic analysis over time, and proviral methylation was determined by Southern blotting and bisulfite methylation mapping. Shortly after infection, proviral expression was inducible and the reporter gene and proviral enhancer showed a low density of methylation. Over time, the efficacy of drug induction diminished, coincident with the accumulation of methyl-CpGs across the provirus. Bisulfite analysis of cells in which 5-azacytidine ***treatment*** induced GFP expression revealed measurable but incomplete demethylation of the provirus. Repression could be overcome in late-passage clones only by pretreatment with 5-azacytidine followed by ***trichostatin*** ***A*** , suggesting that partial demethylation reestablishes the trichostatin-inducible state. These experiments reveal the presence of a silencing mechanism which acts on densely methylated DNA and appears to function independently of ***histone*** ***deacetylase*** activity.

L13 ANSWER 22 OF 27 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:301438 BIOSIS
DOCUMENT NUMBER: PREV200100301438
TITLE: Decitabine and sodium butyrate reactivate expression of a silenced Stat-1 and enhance interferon-responsiveness in the HS-Sultan cell line.
AUTHOR(S): Lavelle, Donald (1); Chen, Yi-Hsiang (1); Hankewych, Maria (1); Kourznetsova, Tatiana (1); DeSimone, Joseph (1)
CORPORATE SOURCE: (1) Medicine, Westside Division, VA Chicago, University of Illinois at Chicago, Chicago, IL USA
SOURCE: Blood, (November 16, 2000) Vol. 96, No. 11 Part 1, pp. 302a. print.
Meeting Info.: 42nd Annual Meeting of the American Society of Hematology San Francisco, California, USA December 01-05, 2000 American Society of Hematology
. ISSN: 0006-4971.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Silencing of Stat-1 gene expression may mediate changes in the growth, survival, and response to interferon of ***cancer*** cells. The level of expression of Stat-1, Stat-2, Stat-3, and Stat-5 in five human myeloma cell lines (ARH-77, HS-Sultan, OPM-2, RPMI 8226, U266) was measured to assess whether alterations of Stat gene expression are associated with multiple myeloma. Constitutive expression of these genes was observed by Western blot analysis in all lines except HS-Sultan, in which the expression of Stat-1 was nearly undetectable. ***Treatment*** of HS-Sultan cells with the DNA methyltransferase ***inhibitor*** 5-aza-2'-deoxycytidine (***decitabine*** ; DAC) and the ***histone*** ***deacetylase*** ***inhibitors*** , sodium ***butyrate*** and ***trichostatin*** ***A*** , reactivated Stat-1 mRNA and protein expression as observed by Northern and Western blot analysis. The addition of interferon-alpha resulted in phosphorylation of the Stat-1 protein in HS-Sultan cells pretreated with either ***decitabine*** or sodium ***butyrate*** . These results suggest that expression of the Stat-1 gene

was silenced by DNA hypermethylation in the HS-Sultan line. The effect of reactivation of Stat-1 expression on the ability of interferon-alpha to inhibit cell growth was determined by measuring the effect of varying doses of interferon on the growth of untreated control cells compared to cells surviving a 72 hour pretreatment with either ***butyrate*** (1mM) or ***decitabine*** (1 X 10-6M). The percent growth inhibition by interferon-alpha (5000, 1250, 310 U/ml) of control cells was 52.1+-7.0, 43.3+-11.5 and 34.6+-10.9 (n=3), of ***decitabine*** -pretreated cells was 83.2+-6.5, 73.4+-10.1, and 66.0+-17.3 (n=3), and of ***butyrate*** -pretreated cells was 79, 65, and 63 (n=1) at the respective doses of interferon. Pretreatment of HS-Sultan with ***decitabine*** or ***butyrate*** , which results in reactivation of Stat-1 expression, thus also increases the response to interferon-alpha.

L13 ANSWER 23 OF 27 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:305376 BIOSIS
DOCUMENT NUMBER: PREV200100305376
TITLE: A phase IIb trial of all-trans retinoic acid (ATRA) combined with bryostatin 1 (BRYO) in patients (pts) with myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML.
AUTHOR(S): Stone, Richard (1); DeAngelo, Daniel (1); Galinsky, Ilene (1); Yang, Xinping (1); Daftary, Farah (1); Xu, Guangin (1); Liou, Simon (1)
CORPORATE SOURCE: (1) Dana-Farber Cancer Institute, Boston, MA USA
SOURCE: Blood, (November 16, 2000) Vol. 96, No. 11 Part 2, pp. 265b. print.
Meeting Info.: 42nd Annual Meeting of the American Society of Hematology San Francisco, California, USA December 01-05, 2000 American Society of Hematology
. ISSN: 0006-4971.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English
AB ATRA, a vitamin A derivative, and BRYO, a macrocyclic lactone isolated from the marine organism B. neritina, synergistically induce monocytic differentiation in human AML cell lines via up-regulation and activation of protein kinase Cbeta (PKCbeta) which initiates cell signaling cascades. A trial in solid ***tumor*** pts determined the maximally tolerated dose (MTD) of BRYO that could be given with ATRA at its MTD. We performed a randomized phase IIb trial in which pts with MDS or AML (relapsed/refractory and/or not a chemotherapy candidate) were given ATRA (75 mg/m2 po bid on d1-8, 15-22) in combination with BRYO (60 ug/m2 over 30 min or 40 ug/m2/d for 72 h on d 8 and 22). 40 pts (27M/13F; age 38-80; median 68 years) were enrolled (17 with MDS (RAEB/RAEB-T (9); RA/RARS (8)) and 23 with AML (relapsed/refractory (12); initial ***treatment*** (rx) in pts > age 60 years (11))). 38 are evaluable (eval) for toxicity (2 dropped out before BRYO due to sepsis (1) and rapid disease progression (1)) and 36 for response (4 dropped out between d 8-28 due to sepsis, disease progression, or other). While disease-related Gr 3/4 sepsis (9) and GI toxicities (5) were noted, serious study drug-related toxicites were limited to cardiac ischemia (1), severe bone pain (1), and BRYO 30 min infusion-related facial flushing and shortness of breath (4) which did not recur upon rechallenge in 3. Although there were no complete or partial remissions, 9 (25% of eval pts, 5 in the BRYO 30 min arm) experienced a sustained improvement by at least 50% in at least one parameter; 8 had a reduction in bone marrow blasts and 5 had an improvement in a cytopenia. 8 pts received at least one additional 22 d cycle. The PKCbeta protein level in ficoll-isolated blood mononuclear cells (MNCs), measured by Western blotting of cytoplasmic extracts compared to an actin control, was down-regulated in the cytoplasm (which correlates with enzyme activation) after 15-45 min relative to the start of BRYO rx in 11/11 pts who received BRYO over 30 min and after 1-3d in 7/11 courses in 7 pts who received the 72 h infusion. These results demonstrate that ATRA in combination with BRYO (at both 30 min and 72 h infusion duration) is well tolerated in pts with MDS and AML, has the predicted effect on PKCbeta levels and posesses some clinical activity. Future trials of this combination plus other differentiation inducers, including ***histone*** ***deacetylase*** or ***DNA*** ***methylation*** ***inhibitors*** , may be warranted.

L13 ANSWER 24 OF 27 MEDLINE DUPLICATE 16

ACCESSION NUMBER: 2000090221 MEDLINE
DOCUMENT NUMBER: 20090221 PubMed ID: 10626795
TITLE: DNA methylation analysis of the promoter region of the human telomerase reverse transcriptase (hTERT) gene.
AUTHOR: Devereux T R; Horikawa I; Anna C H; Annab L A; Afshari C A; Barrett J C
CORPORATE SOURCE: Laboratory of Molecular Carcinogenesis, National Institute of Environmental Health Sciences, NIH, Research Triangle Park, North Carolina 27709, USA.. devereux@niehs.nih.gov
SOURCE: CANCER RESEARCH, (1999 Dec 15) 59 (24) 6087-90.
Journal code: 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200001
ENTRY DATE: Entered STN: 20000204
Last Updated on STN: 20020420
Entered Medline: 20000124

AB The promoter of the hTERT gene encoding the catalytic subunit of telomerase was recently cloned and has a dense CG-rich CpG island, suggesting a role for methylation in regulation of hTERT expression. In this study, we have initiated the analysis of the regulation of hTERT expression by examining the methylation status of up to 72 CpG sites extending from 500 bases upstream of the transcriptional start site of the hTERT gene into the first exon in 37 cell lines. These cell lines represent a variety of cell and tissue types, including normal, immortalized, and ***cancer*** cell lines from lung, breast, and other tissues. Using bisulfite genomic sequencing, we did not find a generalized pattern of site-specific or region-specific methylation that correlated with expression of the hTERT gene: most of the hTERT-negative normal cells and about one-third of the hTERT-expressing cell lines had the unmethylated/hypomethylated promoter, whereas the other hTERT-expressing cell lines showed partial or total methylation of the promoter. The promoter of one hTERT-negative fibroblast cell line, SUSM-1, was methylated at all sites examined. ***Treatment*** of SUSM-1 cells with the demethylating agent 5-aza-2'-deoxycytidine and the ***histone*** ***deacetylase*** ***inhibitor*** ***trichostatin*** ***A*** induced the cells to express hTERT, suggesting a potential role for ***DNA*** ***methylation*** and/or histone deacetylation in negative regulation of hTERT. This study indicates that there are multiple levels of regulation of hTERT expression in CpG island methylation-dependent and -independent manners.

L13 ANSWER 25 OF 27 MEDLINE DUPLICATE 17
ACCESSION NUMBER: 1999113838 MEDLINE
DOCUMENT NUMBER: 99113838 PubMed ID: 9916800
TITLE: Synergy of demethylation and histone deacetylase inhibition in the re-expression of genes silenced in cancer.
AUTHOR: Cameron E E; Bachman K E; Myohanen S; Herman J G; Baylin S B
CORPORATE SOURCE: The Oncology Center, Predoctoral Training Program in Human Genetics, The Johns Hopkins University School of Medicine, Baltimore, Maryland 21231, USA.
SOURCE: NATURE GENETICS, (1999 Jan) 21 (1) 103-7.
Journal code: 9216904. ISSN: 1061-4036.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199902
ENTRY DATE: Entered STN: 19990223
Last Updated on STN: 19990223
Entered Medline: 19990210

AB Densely methylated DNA associates with transcriptionally repressive chromatin characterized by the presence of underacetylated histones. Recently, these two epigenetic processes have been dynamically linked. The methyl-CpG-binding protein MeCP2 appears to reside in a complex with ***histone*** ***deacetylase*** activity. MeCP2 can mediate formation of transcriptionally repressive chromatin on methylated promoter templates in vitro, and this process can be reversed by ***trichostatin*** ***A*** (TSA), a specific ***inhibitor*** of

histone ***deacetylase*** . Little is known, however, about the relative roles of methylation and ***histone*** ***deacetylase*** activity in the stable inhibition of transcription on densely methylated endogenous promoters, such as those for silenced alleles of imprinted genes, genes on the female inactive X chromosome and tumour-suppressor genes inactivated in ***cancer*** cells. We show here that the hypermethylated genes MLH1, TIMP3 (TIMP3), CDKN2B (INK4B, p15) and CDKN2A (INK4, p16) cannot be transcriptionally reactivated with TSA alone in tumour cells in which we have shown that TSA alone can upregulate the expression of non-methylated genes. Following minimal demethylation and slight gene reactivation in the presence of low dose 5-aza-2'deoxycytidine (5Aza-dC), however, TSA ***treatment*** results in robust re-expression of each gene. TSA does not contribute to demethylation of the genes, and none of the ***treatments*** alter the chromatin structure associated with the hypermethylated promoters. Thus, although ***DNA*** ***methylation*** and histone deacetylation appear to act as synergistic layers for the silencing of genes in ***cancer*** , dense CpG island methylation is dominant for the stable maintenance of a silent state at these loci.

L13 ANSWER 26 OF 27 MEDLINE DUPLICATE 18
ACCESSION NUMBER: 90001559 MEDLINE
DOCUMENT NUMBER: 90001559 PubMed ID: 2790198
TITLE: Monocytoid differentiation of freshly isolated human myeloid leukemia cells and HL-60 cells induced by the glutamine antagonist acivicin.
AUTHOR: Nichols K E; Chitneni S R; Moore J O; Weinberg J B
CORPORATE SOURCE: VA Medical Center, Division of Hematology/Oncology, Durham, NC.
CONTRACT NUMBER: AI23308 (NIAID)
AR39162 (NIAMS)
CA09307 (NCI)
SOURCE: BLOOD, (1989 Oct) 74 (5) 1728-37.
Journal code: 7603509. ISSN: 0006-4971.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 198911
ENTRY DATE: Entered STN: 19900328
Last Updated on STN: 19970203
Entered Medline: 19891101

AB Previously we showed that starvation of HL-60 promyelocytic ***leukemia*** cells for a single essential amino acid induced irreversible differentiation into more mature monocyte-like cells. Although not an essential amino acid, glutamine is important in the growth of normal and neoplastic cells. The glutamine analogue, alpha S,5S-alpha-amino-3-chloro-4,5-dihydro-5-isoxazoleacetic acid (acivicin) inhibits several glutamine-utilizing enzymes and therefore depletes cells of certain metabolic end products. The current study was designed to examine in vitro the effects of acivicin on growth and differentiation of several established human myeloid ***leukemia*** cell lines, including the HL-60 cell line, and of freshly isolated cells from patients with acute nonlymphocytic ***leukemia*** (ANLL). Four-day culture of HL-60 cells with acivicin at concentrations of 0.1 to 10.0 micrograms/mL (0.56 to 56 nmol/L) decreased cell growth by 33% to 88% as compared with untreated control cells. Viability of cells was greater than 92% for untreated cells and 93% to 41% for acivicin- ***treated*** cells. Cells ***treated*** with acivicin differentiated along a monocytic pathway as shown by increased H2O2 production and alpha-naphthyl ***butyrate*** esterase (NSE) content. Differentiation was time and dose dependent, and was irreversible. Changes in H2O2 production and NSE content were partially abrogated by co-culture with 10 mmol/L exogenous ***cytidine*** and guanosine but not by co-culture with other nucleosides or glutamine. At these concentrations of acivicin, differentiation was associated with expression of the N-formyl-methyl-leucyl-phenylalanine-receptor (FMLP-R) on 8% to 29% of cells as compared with 8% for control cells. Acivicin potentiated the differentiating effects of interferon-gamma, ***tumor*** necrosis factor, dihydroxyvitamin D3, dimethylsulfoxide, and retinoic acid. Culture of cells from the U937 (monoblastic), K562 (erythroleukemia), and KG-1 (myeloblastic) cell lines resulted in decreased growth and viability, but

not consistently in differentiation. Acivicin decreased survival of freshly isolated ANLL cells and increased their H2O2 production and NSE content. These results suggest that the glutamine analogue acivicin may be useful as a differentiating agent with antileukemia activity in patients with ANLL.

L13 ANSWER 27 OF 27 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1980:259541 BIOSIS
DOCUMENT NUMBER: BA70:52037
TITLE: INHIBITION BY DEOXY CYTIDINE CYTIDINE AND BETA CYTOSINE ARABINOSIDE OF THE INDUCTION OF ALKALINE PHOSPHATASE ACTIVITY IN HELA CELLS.
AUTHOR(S): GOZ B; ORR C; WHARTON W
CORPORATE SOURCE: DEP. PHARMACOL., UNIV. N.C., SCH. MED., CHAPEL HILL, N.C. 27514, USA.
SOURCE: J NATL CANCER INST, (1980) 64 (6), 1355-1362.
CODEN: JNCIAM. ISSN: 0027-8874.
FILE SEGMENT: BA; OLD
LANGUAGE: English
AB Whether the induction of alkaline phosphatase activity in HeLa [human cervical ***carcinoma***] cells by 5-iodo-2'-deoxyuridine (IdUrd) depends on the incorporation of IdUrd into DNA was examined. Tymidine (dThd), deoxycytidine (dCyd), ***cytidine*** and .beta.-cytosine arabinoside (Ara-C) inhibited in a dose-dependent manner the induction of alkaline phosphatase activity by IdUrd in HeLa cells; 5-iodo-2'-deoxycytidine induced activity in a dose-dependent manner at concentrations similar to those of IdUrd. Three of these compounds (dThd, dCyd and Ara-C) were studied with regard to degree of inhibition of induction and IdUrd incorporation into DNA. Although the various doses of these 3 compounds decreased the incorporation of IdUrd into DNA, there was no apparent linear correlation between the extent of inhibition of IdUrd incorporation and the degree of inhibition of the induction of alkaline phosphatase activity. dCyd inhibited in a dose-dependent manner the induction of alkaline phosphatase by hydrocortisone, soldium ***butyrate*** and choline chloride. The idea that IdUrd induction of alkaline phosphatase activity in HeLa cells does not require IdUrd incorporation into DNA is supported. dCyd altered the thermostability for alkaline phosphatase activity from control or IdUrd- ***treated*** cells; for control cells the change in thermostability occurred without a change in the enzyme-specific activity.

=> d his

(FILE 'HOME' ENTERED AT 19:31:41 ON 21 NOV 2002)

FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH, AGRICOLA' ENTERED AT 19:32:09 ON 21 NOV 2002
L1 5184193 S CANCER OR CARCINOMA OR SARCOMA OR TUMOR OR MALIGNANT OR LEUKE
L2 1777 S (DNA METHYLATION) (P) INHIBITOR
L3 32691 S CYTIDINE OR DECITABINE
L4 34371 S L2 OR L3
L5 3671 S (HISTONE DEACETYLASE) (P) INHIBITOR
L6 16304 S (HYDROXAMIC ACID) OR (TRICHOSTATIN A) OR OXAMFLATIN OR PYROXA
L7 4070 S (TRAPOXIN A) OR APICIDIN OR DEPSIPEPTIDE OR FR901228
L8 27241 S BENZAMIDE OR MS-27-275
L9 105163 S BUTYRATE OR (BUTYRIC ACID) OR PHENYLUTYRATE OR (ARGININE BUTY
L10 152314 S L5 OR L6 OR L7 OR L8 OR L9
L11 155 S L1 (P) L4 (P) L10
L12 95 S L11 (P) TREAT?
L13 27 DUPLICATE REMOVE L12 (68 DUPLICATES REMOVED)

=> duplicate remove l11
DUPLICATE PREFERENCE IS 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH'
KEEP DUPLICATES FROM MORE THAN ONE FILE? Y/(N):n
PROCESSING COMPLETED FOR L11
L14 50 DUPLICATE REMOVE L11 (105 DUPLICATES REMOVED)

=> s l14 not l13
L15 23 L14 NOT L13

=> d l15 1-23 ibib abs

L15 ANSWER 1 OF 23 MEDLINE
ACCESSION NUMBER: 2002642680 IN-PROCESS
DOCUMENT NUMBER: 22289349 PubMed ID: 12198113
TITLE: Regulation of DNA Methylation in Human Breast Cancer. EFFECT ON THE UROKINASE-TYPE PLASMINOGEN ACTIVATOR GENE PRODUCTION AND TUMOR INVASION.
AUTHOR: Guo Yongjing; Pakneshan Pouya; Gladu Julienne; Slack Andrew; Szyf Moshe; Rabbani Shafaat A
CORPORATE SOURCE: Departments of Medicine and Pharmacology, McGill University Health Center, Montreal, Quebec H3A 1A1, Canada.
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (2002 Nov 1) 277 (44) 41571-9.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20021029
Last Updated on STN: 20021029

AB Urokinase-type plasminogen activator (uPA) is a member of the serine protease family and can break down various components of the extracellular matrix to promote growth, invasion, and metastasis of several malignancies including breast ***cancer*** . In the current study we examined the role that the ***DNA*** ***methylation*** machinery might be playing in regulating differential uPA gene expression in breast ***cancer*** cell lines. uPA mRNA is expressed in the highly invasive, hormone-insensitive human breast ***cancer*** cell line MDA-MB-231 but not in hormone-responsive cell line MCF-7. Using methylation-sensitive PCR, we show that 90% of CpG dinucleotides in the uPA promoter are methylated in MCF-7 cells, whereas fully demethylated CpGs were detected in MDA-MB-231 cells. uPA promoter activity, which is directly regulated by the Ets-1 transcription factor, is inhibited by methylation as determined by uPA promoter-luciferase reporter assays. We then tested whether the state of expression and methylation of the uPA promoter correlates with the global level of DNA methyltransferase and demethylase activities in these cell lines. We show that maintenance DNA methyltransferase activity is significantly higher in MCF-7 cells than in MDA-MB-231 cells, whereas demethylase activity is higher in MDA-MB-231 cells. We suggest that the combination of increased DNA methyltransferase activity with reduced demethylase activity contributes to the methylation and silencing of uPA expression in MCF-7 cells. The converse is true in MDA-MB-231 cells, which represents a late stage highly invasive breast ***cancer*** . The ***histone*** ***deacetylase*** ***inhibitor*** , ***Trichostatin*** ***A*** , induces the expression of the uPA gene in MDA-MB-231 cells but not in MCF-7 cells. This supports the hypothesis that ***DNA*** ***methylation*** is the dominant mechanism involved in the silencing of uPA gene expression. Taken together, these results provide insight into the mechanism regulating the transcription of the uPA gene in the complex multistep process of breast ***cancer*** progression.

L15 ANSWER 2 OF 23 MEDLINE
ACCESSION NUMBER: 2002634371 IN-PROCESS
DOCUMENT NUMBER: 22280221 PubMed ID: 12394273
TITLE: Antineoplastic action of 5-aza-2'-deoxycytidine and phenylbutyrate on human lung carcinoma cells.
AUTHOR: Boivin Anne-Julie; Momparler Louise F; Hurtubise Annie; Momparler Richard L
CORPORATE SOURCE: Departement de Pharmacologie, Universite de Montreal and Centre de Recherche Pediatrique, Hopital Sainte-Justine, Montreal, Quebec H3T 1C5, Canada.
SOURCE: ANTI-CANCER DRUGS, (2002 Sep) 13 (8) 869-74.
Journal code: 9100823. ISSN: 0959-4973.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20021024
Last Updated on STN: 20021024

AB Current chemotherapy of advanced non-small cell lung ***cancer*** produces only a modest increase in survival time. New approaches are

needed to improve its effectiveness. During tumorigenesis, silencing of ***tumor*** suppressor genes can occur by aberrant methylation. The ***DNA*** ***methylation*** ***inhibitor*** , 5-aza-2'-deoxycytidine (5-AZA-CdR), can reactivate the expression of these genes. Nucleosomes containing unacetylated positively charged histones bind tightly to DNA producing a compact configuration, which inhibits transcription. Phenylbutyrate (PB), an ***inhibitor*** of ***histone*** ***deacetylase*** (HDAC), increases histone acetylation, neutralizing its positive charge and resulting in DNA with a more open structure, which favors transcription. It has been reported that 5-AZA-CdR in combination with HDAC ***inhibitor*** can increase the expression of silent ***tumor*** suppressor genes. The objective of our study was to determine if these agents, in combination, produce an enhancement of their antitumor activity. We evaluated the antineoplastic activity of 5-AZA-CdR and PB alone or in combination on human A549 and Calu-6 lung ***carcinoma*** cell lines by inhibition of DNA synthesis and clonogenic assays. 5-AZA-CdR and PB in combination produced a greater inhibition of DNA synthesis than either agent alone. Also, in a clonogenic assay the combination of these drugs showed a significant synergistic antitumor effect. These results provide a rationale to investigate the combination of 5-AZA-CdR and PB in patients with advanced lung ***cancer*** .

L15 ANSWER 3 OF 23 MEDLINE
ACCESSION NUMBER: 2002357270 MEDLINE
DOCUMENT NUMBER: 22095552 PubMed ID: 11978794
TITLE: The oncoprotein Set/TAF-1beta, an inhibitor of histone acetyltransferase, inhibits active demethylation of DNA, integrating DNA methylation and transcriptional silencing.
AUTHOR: Cervoni Nadia; Detich Nancy; Seo Sang-Beom; Chakravarti Debabrata; Szyf Moshe
CORPORATE SOURCE: Department of Pharmacology and Therapeutics, McGill University, Montreal, Quebec H3G 1Y6, Canada.
CONTRACT NUMBER: R01 DK57079 (NIDDK)
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (2002 Jul 12) 277 (28) 25026-31.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200208
ENTRY DATE: Entered STN: 20020709
Last Updated on STN: 20020813
Entered Medline: 20020812

AB Histone hypoacetylation and DNA hypermethylation are hallmarks of gene silencing. Although a role for ***DNA*** ***methylation*** in regulating histone acetylation has been established, it is not clear how and whether epigenetic histone markings influence DNA modifications in transcriptional silencing. We have previously shown that induction of histone acetylation by ***trichostatin*** ***A*** promotes demethylation of ectopically methylated DNA (Cervoni, N., and Szyf, M. (2001) J. Biol. Chem. 276, 40778-40787). The oncoprotein Set/TAF-Ibeta is a subunit of the recently identified ***inhibitor*** of acetyltransferases complex that inhibits histone acetylation by binding to and masking histone acetyltransferase targets (Seo, S. B., McNamara, P., Heo, S., Turner, A., Lane, W. S., and Chakravarti, D. (2001) Cell 104, 119-130). We show here that the overexpression of Set/TAF-Ibeta, whose expression is up-regulated in multiple ***tumor*** tissues, inhibits demethylation of ectopically methylated DNA resulting in gene silencing. Overexpression of a mutant Set/TAF-Ibeta that does not inhibit histone acetylation is defective in inhibiting DNA demethylation. Taken together, these results are consistent with a novel regulatory role for Set/TAF-Ibeta, integrating epigenetic states of histones and DNA in gene regulation and provide a new mechanism that can explain how hypermethylation of specific regions might come about by inhibition of demethylation in ***cancer*** cells.

L15 ANSWER 4 OF 23 MEDLINE
ACCESSION NUMBER: 2001673186 MEDLINE
DOCUMENT NUMBER: 21575860 PubMed ID: 11719467
TITLE: Heterogeneous transforming growth factor (TGF)-beta

activation, whereas conversely, deacetylation of histones is associated with gene silencing and transcriptional repression. Here we report that ***inhibitors*** of ***histone*** ***deacetylase*** (HDAC), ***depsipeptide*** and ***trichostatin*** ***A*** , induce apoptotic cell death in human lung ***cancer*** cells as demonstrated by DNA flow cytometry and Western immunoblot to detect cleavage of poly(ADP-ribose) polymerase. This HDAC inhibitorinduced apoptosis is greatly enhanced in the presence of the DNA methyltransferase ***inhibitor*** , 5-aza-2'-deoxycytidine (DAC). The HDAC ***inhibitor*** -induced apoptosis appears to be p53 independent, because no change in apoptotic cell death was observed in H1299 cells that expressed exogenous wild-type p53 (H1299 cells express no endogenous p53 protein). To further investigate the mechanism of DAC-enhanced, HDAC ***inhibitor*** -induced apoptosis, we analyzed histone H3 and H4 acetylation by Western immunoblotting. Results showed that ***depsipeptide*** induced a dose-dependent acetylation of histones H3 and H4, which was greatly increased in DAC-pretreated cells. By analyzing the acetylation of specific lysine residues at the amino terminus of histone H4 (Ac-5, Ac-8, Ac-12, and Ac-16), we found that the enhancement of HDAC ***inhibitor*** -induced acetylation of histones in the DAC-pretreated cells was not lysine site specific. These results demonstrate that ***DNA*** ***methylation*** status is an important determinant of apoptotic susceptibility to HDAC ***inhibitors*** .

L15 ANSWER 6 OF 23 MEDLINE
ACCESSION NUMBER: 2001153834 MEDLINE
DOCUMENT NUMBER: 21039633 PubMed ID: 11196471
TITLE: Mechanisms of epigenetic silencing of the c21 gene in Y1 adrenocortical tumor cells.
AUTHOR: Szyf M; Slack A D
CORPORATE SOURCE: Department of Pharmacology and Therapeutics, McGill University, Montreal, Quebec, Canada.. mszyf@pharma.mcgill.ca
SOURCE: ENDOCRINE RESEARCH, (2000 Nov) 26 (4) 921-30. Journal code: 8408548. ISSN: 0743-5800.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200103
ENTRY DATE: Entered STN: 20010404
Last Updated on STN: 20010404
Entered Medline: 20010322
AB We utilized Y1 adrenocortical ***carcinoma*** cell line as a model system to dissect the events regulating epigenomic gene silencing in ***tumor*** cells. We show here that the chromatin structure of c21 gene is inactive in Y1 cells and that it could be reconfigured to an active form by either expressing antisense mRNA to DNA methyltransferase 1 (dnmt1) or an attenuator of Ras protooncogenic signaling hGAP. Surprisingly however, the known inducer of active chromatin structure the ***histone*** ***deacetylase*** ***inhibitor*** ***trichostatin*** ***A*** TSA fails to induce expression of c21. These results suggest that the primary cause of c21 gene silencing is independent of histone deacetylation. We present a model to explain the possible roles of the different components of the epigenome and the ***DNA*** ***methylation*** and demethylation machineries in silencing c21 gene expression.

L15 ANSWER 7 OF 23 MEDLINE
ACCESSION NUMBER: 2000501591 MEDLINE
DOCUMENT NUMBER: 20500518 PubMed ID: 11049023
TITLE: Novel therapeutic agents for the treatment of myelodysplastic syndromes.
AUTHOR: Cheson B D; Zwiebel J A; Dancey J; Murgo A
CORPORATE SOURCE: Cancer Therapy Evaluation Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute, Bethesda, MD 20892, USA.
SOURCE: SEMINARS IN ONCOLOGY, (2000 Oct) 27 (5) 560-77. Ref: 192 Journal code: 0420432. ISSN: 0093-7754.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200011
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001102

AB Few chemotherapy agents have demonstrated activity in patients with myelodysplastic syndromes (MDS) and supportive management remains the standard of care. An increasing number of new drugs in development are being directed at specific molecular or biological targets of these diseases. Topotecan, a topoisomerase I ***inhibitor*** , has shown single-agent activity and is now being combined with other agents, including cytarabine. The aminothiol amifostine induces responses in about 30% of patients; however, its role is still being clarified. Agents that inhibit ***histone*** ***deacetylase*** and target DNA hypermethylation, thus permitting derepression of normal genes, include 5-azacytidine, ***decitabine*** , phenylbutyrate, and ***depsipeptide*** . Arsenic trioxide has demonstrated impressive activity in acute promyelocytic ***leukemia*** and preclinical data suggest the potential for activity in MDS. UCN-01 is a novel agent that inhibits protein kinase C and other protein kinases important for progression through the G1 and G2 phases of the cell cycle. Dolastatin-10 has extremely potent in vitro activity against a variety of ***tumor*** cell lines. Since its dose-limiting toxicities include myelosuppression, it is being studied in acute myelogenous ***leukemia*** (AML) and MDS. Ras may play a role in MDS, and activation of this gene and its signaling pathways may require farnesylation. Several farnesyl transferase ***inhibitors*** are now available for study in patients with MDS. An increasing body of data suggests a possible role for angiogenesis in MDS, and several antiangiogenesis agents are in clinical trials, including thalidomide, SU5416, and anti-vascular endothelial growth factor (VEGF) antibodies. Development of new drugs and regimens will be facilitated by recently developed standardized response criteria. Future clinical trials should focus on rational combinations of these agents and others with the goal of curing patients with MDS.

L15 ANSWER 8 OF 23 MEDLINE
ACCESSION NUMBER: 2000221577 MEDLINE
DOCUMENT NUMBER: 20221577 PubMed ID: 10757815
TITLE: Methylation of the cyclin A1 promoter correlates with gene silencing in somatic cell lines, while tissue-specific expression of cyclin A1 is methylation independent.
AUTHOR: Muller C; Readhead C; Diederichs S; Idos G; Yang R; Tidow N; Serve H; Berdel W E; Koeffler H P
CORPORATE SOURCE: Division of Hematology/Oncology, Cedars-Sinai Research Institute/UCLA School of Medicine, Los Angeles, California 90048, USA.. muellerc@uni-muenster.de
CONTRACT NUMBER: 1RO1R12406
SOURCE: MOLECULAR AND CELLULAR BIOLOGY, (2000 May) 20 (9) 3316-29. Journal code: 8109087. ISSN: 0270-7306.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200005
ENTRY DATE: Entered STN: 20000525
Last Updated on STN: 20000525
Entered Medline: 20000515

AB Gene expression in mammalian organisms is regulated at multiple levels, including DNA accessibility for transcription factors and chromatin structure. Methylation of CpG dinucleotides is thought to be involved in imprinting and in the pathogenesis of ***cancer*** . However, the relevance of methylation for directing tissue-specific gene expression is highly controversial. The cyclin A1 gene is expressed in very few tissues, with high levels restricted to spermatogenesis and leukemic blasts. Here, we show that methylation of the CpG island of the human cyclin A1 promoter was correlated with nonexpression in cell lines, and the methyl-CpG binding protein MeCP2 suppressed transcription from the methylated cyclin A1 promoter. Repression could be relieved by ***trichostatin*** ***A*** . Silencing of a cyclin A1 promoter-enhanced green fluorescent

protein (EGFP) transgene in stable transfected MG63 osteosarcoma cells was also closely associated with de novo promoter methylation. Cyclin A1 could be strongly induced in nonexpressing cell lines by ***trichostatin*** ***A*** but not by 5-aza- ***cytidine*** . The cyclin A1 promoter-EGFP construct directed tissue-specific expression in male germ cells of transgenic mice. Expression in the testes of these mice was independent of promoter methylation, and even strong promoter methylation did not suppress promoter activity. MeCP2 expression was notably absent in EGFP-expressing cells. Transcription from the transgenic cyclin A1 promoter was repressed in most organs outside the testis, even when the promoter was not methylated. These data show the association of methylation with silencing of the cyclin A1 gene in ***cancer*** cell lines. However, appropriate tissue-specific repression of the cyclin A1 promoter occurs independently of CpG methylation.

L15 ANSWER 9 OF 23 MEDLINE
ACCESSION NUMBER: 2000139833 MEDLINE
DOCUMENT NUMBER: 20139833 PubMed ID: 10676663
TITLE: Drg-1 as a differentiation-related, putative metastatic suppressor gene in human colon cancer.
AUTHOR: Guan R J; Ford H L; Fu Y; Li Y; Shaw L M; Pardee A B
CORPORATE SOURCE: Division of Gastroenterology, Brigham and Women's Hospital, Dana-Farber Cancer Institute, Boston, Massachusetts 02115, USA.
CONTRACT NUMBER: R0-1 CA61253 (NCI)
SOURCE: CANCER RESEARCH, (2000 Feb 1) 60 (3) 749-55.
Journal code: 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200002
ENTRY DATE: Entered STN: 20000314
Last Updated on STN: 20000314
Entered Medline: 20000228
AB A gene related to cell differentiation was identified by differential display as a candidate suppressor of metastases in colon ***cancer*** . This gene, with a full-length cDNA of 3 kb, is expressed in normal colon and primary colon ***cancer*** tissues and cell lines but not in their metastatic counterparts. A GenBank search found that it is identical to a recently cloned gene, differentiation-related gene-1 (Drg-1), isolated from differentiated HT-29 colon ***cancer*** cells. Stable transfection of the SW620 metastatic colon ***cancer*** cell line with Drg-1 cDNA induced morphological changes consistent with differentiation and up-regulated the expression of several colonic epithelial cell differentiation markers (alkaline phosphatase, carcinoembryonic antigen, and E-cadherin). Moreover, the expression of Drg-1 is controlled by several known cell differentiation reagents, such as ligands of peroxisome proliferator-activated receptor gamma (troglitazone and BRL46593) and of retinoid X receptor (LG268), and ***histone*** ***deacetylase*** ***inhibitors*** (***trichostatin*** ***A*** , suberoylanilide ***hydroxamic*** ***acid*** , and tributyrin). A synergistic induction of Drg-1 expression was seen with the combination of tributyrin and a low dose of 5'-aza-2'-dexoycytidine (100 nM), an ***inhibitor*** of ***DNA*** ***methylation*** . Functional studies revealed that overexpression of Drg-1 in metastatic colon ***cancer*** cells reduced in vitro invasion through Matrigel and suppressed in vivo liver metastases in nude mice. We propose that Drg-1 suppresses colon ***cancer*** metastasis by inducing colon ***cancer*** cell differentiation and partially reversing the metastatic phenotype.

L15 ANSWER 10 OF 23 MEDLINE
ACCESSION NUMBER: 95341856 MEDLINE
DOCUMENT NUMBER: 95341856 PubMed ID: 7616736
TITLE: Mechanistic considerations in chemopreventive drug development.
AUTHOR: Kelloff G J; Boone C W; Steele V E; Fay J R; Lubet R A; Crowell J A; Sigman C C
CORPORATE SOURCE: Chemoprevention Branch, Division of Cancer Prevention and Control (DCPC), National Cancer Institute (NCI), Bethesda, MD 20892, USA.
SOURCE: JOURNAL OF CELLULAR BIOCHEMISTRY. SUPPLEMENT, (1994) 20

1-24. Ref: 297
Journal code: 8207539. ISSN: 0733-1959.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199508
ENTRY DATE: Entered STN: 19950905
Last Updated on STN: 19950905
Entered Medline: 19950824

AB This overview of the potential mechanisms of chemopreventive activity will provide the conceptual groundwork for chemopreventive drug discovery, leading to structure-activity and mechanistic studies that identify and evaluate new agents. Possible mechanisms of chemopreventive activity with examples of promising agents include carcinogen blocking activities such as inhibition of carcinogen uptake (calcium), inhibition of formation or activation of carcinogen (arylalkyl isothiocyanates, DHEA, NSAIDs, polyphenols), deactivation or detoxification of carcinogen (oltipraz, other GSH-enhancing agents), preventing carcinogen binding to DNA (oltipraz, polyphenols), and enhancing the level or fidelity of DNA repair (NAC, protease ***inhibitors***). Chemopreventive antioxidant activities include scavenging reactive electrophiles (GSH-enhancing agents), scavenging oxygen radicals (polyphenols, vitamin E), and inhibiting arachidonic acid metabolism (glycyrrhetinic acid, NAC, NSAIDs, polyphenols, tamoxifen). Antiproliferation/antiprogression activities include modulation of signal transduction (glycyrrhetinic acid, NSAIDs, polyphenols, retinoids, tamoxifen), modulation of hormonal and growth factor activity (NSAIDs, retinoids, tamoxifen), inhibition of aberrant oncogene activity (genistein, NSAIDs, monoterpenes), inhibition of polyamine metabolism (DFMO, retinoids, tamoxifen), induction of terminal differentiation (calcium, retinoids, vitamin D3), restoration of immune response (NSAIDs, selenium, vitamin E), enhancing intercellular communication (carotenoids, retinoids), restoration of ***tumor*** suppressor function, induction of programmed cell death (apoptosis) (***butyric*** ***acid*** , genistein, retinoids, tamoxifen), correction of ***DNA*** ***methylation*** imbalances (folic acid), inhibition of angiogenesis (genistein, retinoids, tamoxifen), inhibition of basement membrane degradation (protease ***inhibitors***), and activation of antimetastasis genes. A systematic drug development program for chemopreventive agents is only possible with continuing research into mechanisms of action and thoughtful application of the mechanisms to new drug design and discovery. One approach is to construct pharmacological activity profiles for promising agents. These profiles are compared among the promising agents and with untested compounds to identify similarities. Classical structure-activity studies are used to find optimal agents (high efficacy with low toxicity) based on good lead agents. Studies evaluating tissue-specific and pharmacokinetic parameters are very important. A final approach is design of mechanism-based assays and identification of mechanism-based intermediate biomarkers for evaluation of chemopreventive efficacy.

L15 ANSWER 11 OF 23 MEDLINE
ACCESSION NUMBER: 89008628 MEDLINE
DOCUMENT NUMBER: 89008628 PubMed ID: 2459137
TITLE: Effects of 5-azacytidine, sodium butyrate, and phorbol esters on amino acid transport system A in a kidney epithelial cell line, MDCK: evidence for multiple mechanisms of regulation.
AUTHOR: Boerner P; Saier M H Jr
CORPORATE SOURCE: Department of Biology, University of California, San Diego, La Jolla 92093.
CONTRACT NUMBER: 5R01 AM21994 (NIADDK)
R01 A121702
SOURCE: JOURNAL OF CELLULAR PHYSIOLOGY, (1988 Oct) 137 (1) 117-24.
Journal code: 0050222. ISSN: 0021-9541.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198811

ENTRY DATE: Entered STN: 19900308
Last Update[redacted]n STN: 19990129
Entered Medline: 19881121

AB Neutral amino acid transport by system A was investigated in the epithelial cell lines MDCK and MDCK-T1. The latter line is a chemically induced, oncogenically transformed line derived from MDCK. Inducers of differentiation, sodium ***butyrate*** and 5-azacytidine, and a ***tumor*** promoter, TPA, were used as probes to delineate pathways of regulation involved in system A response to a variety of physiological conditions and agents. Azacytidine, an ***inhibitor*** of ***DNA*** ***methylation*** , and ***butyrate*** , an enhancer of histone acetylation, inhibited expression of system A, had little effect on system ASC, and slightly stimulated system L. Inhibition of system A expression by ***butyrate*** and azacytidine occurred under different conditions. Increases in system A activity due to amino acid starvation or transformation were inhibited by ***butyrate*** but not by azacytidine. Repressed system A activity, normally observed in the presence of high levels of amino acids, was more sensitive to azacytidine than to ***butyrate*** . The ***tumor*** promoter, TPA, stimulated system A activity in MDCK cells under normal growth conditions but did not stimulate activity in amino acid-starved MDCK cells or in MDCK-T1 cells. Stimulation of system A activity by TPA was prevented by prior exposure to ***butyrate*** but not to azacytidine. These results suggest 1) that system A expression observed in growing amino-acid-repressed MDCK cells is modulated by an azacytidine-sensitive mechanism and 2) that the elevated expression of system A activity induced by amino acid starvation, by chemical transformation to MDCK-T1, and by TPA is modulated by a ***butyrate*** -sensitive mechanism.

L15 ANSWER 12 OF 23 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:618078 CAPLUS
TITLE: Histone deacetylase inhibitors and the treatment of cancers
AUTHOR(S): Rifkind, Richard A.; Richon, Victoria; Breslow, Ronald; Marks, Paul A.
CORPORATE SOURCE: The Cell Biology Program, Memorial Sloan-Kettering Cancer Center, New York, NY, 10021, USA
SOURCE: Abstracts of Papers, 224th ACS National Meeting, Boston, MA, United States, August 18-22, 2002 (2002), MEDI-226. American Chemical Society: Washington, D. C.
CODEN: 69CZPZ
DOCUMENT TYPE: Conference; Meeting Abstract
LANGUAGE: English

AB Based upon a strategy of searching for increasingly potent inducers of ***cancer*** cell differentiation cessation of proliferation, and apoptosis, which started with the observation that di-Me sulfoxide, at relatively high molar concn.(250 mM), had such properties, a series of increasingly potent hybrid polar compds. have been synthesized, and the most potent examples of this series have been found to be ***inhibitors*** of class I, II, and III ***histone*** ***deacetylases*** (HDACs). Structure/function anal. combined with x-ray crystallog. studies of the enzyme indicate that the chem. ***inhibitors*** such as suberoyl-analide ***hydroxamic*** ***acid*** (SAHA; effective in vitro at low micromolar concns.)are lysine analogs which insert within the protein's catalytic cleft, and coordinate with the zinc atoms found at the base of that cleft, thereby blocking the activity of the enzyme on its natural substrate, the N-terminal lysines of histone. The net effect measurable as a consequence of this inhibition is the hyperacetylation of histone N-terminal lysines and, apparently, a phys. reorganization of nucleosomal structure. The mol. basis for the selectivity of this effect on gene transcription remains obscure but a role for other epigenetic factors, such as histone and/or ***DNA*** ***methylation*** , remains an important speculation. SAHA and a 2nd HDAC- ***inhibitor*** ***hydroxamic*** ***acid*** , ***pyroxamide*** , have recently entered clin. trials; accumulation of acetylated histone can be detected in the peripheral blood mononuclear cells and in ***tumor*** biopsies obtained from patients receiving SAHA. Phase I studies with i.v. administered SAHA have revealed that it is extremely well tolerated without significant side-effects up to and beyond the dose apparently needed to achieve radiol. measurable ***tumor*** regression and disease stabilization. A parallel phase I

AUTHOR(S): Bovenzi, Veronica (1); Momparler, R. L.
CORPORATE SOURCE: (1) St Jose[illegible]ne Hosp, Montreal, Quebec Cana[illegible]
SOURCE: Proceedings of the American Association for Cancer Research Annual Meeting, (March, 2000) No. 41, pp. 603. print..
Meeting Info.: 91st Annual Meeting of the American Association for Cancer Research. San Francisco, California, USA April 01-05, 2000
ISSN: 0197-016X.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

L15 ANSWER 16 OF 23 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1984:340513 BIOSIS
DOCUMENT NUMBER: BA78:76993
TITLE: DIFFERENTIAL EXPRESSION OF HLA-DR AND HLA-DC-DS MOLECULES IN A PATIENT WITH HAIRY CELL ***LEUKEMIA*** RESTORATION OF HLA-DC-DS EXPRESSION BY 12-O TETRADECANOYL PHORBOL 13 ACETATE 5 AZA ***CYTIDINE*** AND SODIUM ***BUTYRATE*** .
AUTHOR(S): FAILLE A; TURMEL P; CHARRON D J
CORPORATE SOURCE: SERVICE DE MEDECINE NUCLEAIRE DU PROFESSEUR Y. NAJEAN, HOPITAL SAINT-LOUIS, 75475 PARIS, CEDEX 10, FR.
SOURCE: BLOOD, (1984) 64 (1), 33-37.
CODEN: BLOOAW. ISSN: 0006-4971.
FILE SEGMENT: BA; OLD
LANGUAGE: English
AB Biosynthesis and molecular structure of major histocompatibility complex (MHC) class II antigens of DR2/DR7 hairy cells were analyzed by 2-dimensional polyacrylamide-gel electrophoresis (2D-PAGE). Two anti-human Ia monoclonal antibodies (mAb) were used to immunoprecipitate DR and DR-linked DC/DS molecules. Monoclonal antibody VI 15 C recognizes DR (I-E-like) molecules and CA 2.06 precipitates DR and DR-linked DC/DS (I-A-like) molecules in DR7 allotypes. Studies were performed on a pure population of hairy cells before and after culture with phorbol ester:12-O-tetradecanoyl phorbol-13-acetate (TPA), 5-azacytidine (5 Aza), sodium butyrate (NA-BU), and phytohemagglutinin (PHA-P). BEfore any treatment, hairy cells expressed and synthesized DR antigens: DR .alpha. and .beta. subunits appeared both qualitatively and quantitatively normal by 2D-PAGE profile. The hairy cells failed to express and synthesize any DC/DS molecule. The lack of DC/DS molecular expression was restored after culture in presence of TPA, sodium butyrate and 5 azacytidine, but not after PHA-P treatment. Differential molecular expression of MHC class II antigens in leukemic cells provides a model to define further discrete stages of hemopoietic differentiation and study the role of these molecules in the cellular interactions occurring during differentiation.

L15 ANSWER 17 OF 23 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1982:253414 BIOSIS
DOCUMENT NUMBER: BA74:25894
TITLE: INDUCTION OF TARGET ANTIGENS AND CONVERSION TO SUSCEPTIBLE PHENOTYPE OF NATURAL KILLER CELL RESISTANT LYMPHOID CELL LINE.
AUTHOR(S): CLARK E A; STURGE J C; FALK L A JR
CORPORATE SOURCE: REGIONAL PRIMATE RESEARCH CENTER, UNIV. OF WASHINGTON, SEATTLE, WA. 98195.
SOURCE: INT J CANCER, (1981) 28 (5), 647-654.
CODEN: IJCNAW. ISSN: 0020-7136.
FILE SEGMENT: BA; OLD
LANGUAGE: English
AB Two autologous Herpesvirus papio producer lymphoid cell lines and 1 autologous non-producer line were compared for susceptibility to natural killer (NK) cell-mediated lysis. The non-producer cell line, 26CB-1, was more resistant to NK cell killing compared to 1 viral producer counterpart 13CB-1, but equally resistant when compared to another, 8CB-I. Treatment with chemical agents that affect differentiation or activate the viral cycle, including n-butyrate, IuDR, 5-azacytidine and tunicamycin, increased the susceptibility to killing of the non-producer line but had less effect on the 13CB-I producer line. The increase in suscpetiblity was due to induction of new target antigens: activated 26CB-I cells were more effective at inhibiting NK-cell-mediated lysis and were bound by more NK cells than untreated control cells. The expression of NK target structures

may be related to the differentiated state rather than to the viral production status of target cells.

L15 ANSWER 18 OF 23 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1981:275877 BIOSIS
DOCUMENT NUMBER: BA72:60861
TITLE: RAPID ANALYSIS OF DRUG EFFECTS ON THE CELL CYCLE.
AUTHOR(S): DARZYNKIEWICZ Z; TRAGANOS F; XUE S; STAIANO-COICO L; MELAMED M R
CORPORATE SOURCE: MEMORIAL SLOAN-KETTERING CANCER CENTER, NEW YORK, N.Y.
SOURCE: CYTOMETRY, (1981) 1 (4), 279-286.
CODEN: CYTODQ. ISSN: 0196-4763.
FILE SEGMENT: BA; OLD
LANGUAGE: English
AB Using a flow cytometric technique to analyze DNA content and chromatin structure simultaneously, the following parameters of cell cycle progression were estimated in control and drug-treated [mouse leukemia] L1210 cell cultures: the kinetics of cell exit from the G1 phase; the probability of cell exit from the indeterminate portion of the G1 phase, measured as the half-time of cell residence in that state; the duration of the deterministic portion of G1 phase; the rates of cell transit through selected windows in S phase; the rate of cell entrance into mitosis; the mean duration of the cell cycle (Tc). These parameters are obtained in a single stathmokinetic experiment from measurements of individual samples withdrawn at 30 min to 1 h intervals from vinblastine-treated cultures. In the same experiment mitotic indices are obtained with high statistical accuracy, and may be used to determine the terminal point of drug action. In addition to cell cycle analysis the method makes it possible to detect drug-induced changes in nuclear chromatin that are manifested by varying sensitivity of DNA in situ to denaturation by acid. Such changes were associated with defective chromatin condensation, altered histone modifications or intercalation of the drugs into DNA. Using this technique the effects of sodium n-butyrate and 2 new antitumor drugs [dihydroxyanthraquinone and dihydro-5-azacytidine] on L1210 cells were investigated.

L15 ANSWER 19 OF 23 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1981:169453 BIOSIS
DOCUMENT NUMBER: BA71:39445
TITLE: A COLCHICINE SENSITIVE UPTAKE SYSTEM IN MORRIS HEPATOMAS.
AUTHOR(S): TAUBER R; REUTTER W
CORPORATE SOURCE: BIOCHEM. INST., ALBERT-LUDWIGS-UNIV., HERMANN-HERDER-STR. 7, D-7800 FREIBURG, W. GER.
SOURCE: PROC NATL ACAD SCI U S A, (1980) 77 (9), 5282-5286.
CODEN: PNASA6. ISSN: 0027-8424.
FILE SEGMENT: BA; OLD
LANGUAGE: English
AB The interference of microtubular disruptors with the uptake of amino acids and other low MW substrates was studied in rat Morris hepatomas, host liver and regenerating liver. Colchicine inhibits amino acid transport (.alpha.-aminoisobutyric acid, L-methionine and L-leucine) in hepatomas by 59-98%; transport in host and regenerating liver is not impeded but increased. In hepatomas, treatment with colchicine reduces the uptake of L-fucose, cytidine, urea and carbonate. Vinblastine, but not lumicolchicine or cytochalasin B, is an effective inhibitor. The inhibition of uptake is not linked to a decrease of cellular ATP and UTP. Apparently the transport of low MW substrates in hepatomas is related to microtubules or other colchicine-binding structures, e.g., of the plasma membrane. This colchicine-sensitive uptake system in hepatomas may be due to the malignant transformation of hepatocytes.

L15 ANSWER 20 OF 23 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 95115933 EMBASE
DOCUMENT NUMBER: 1995115933
TITLE: Mechanistic considerations in chemopreventive drug development.
AUTHOR: Kelloff G.J.; Boone C.W.; Steele V.E.; Fay J.R.; Lubet R.A.; Crowell J.A.; Sigman C.C.
CORPORATE SOURCE: Chemoprevention Branch, DCPC, National Cancer Institute, 9000 Rockville Pike,Bethesda, MD 20892, United States
SOURCE: Journal of Cellular Biochemistry, (1994) 56/SUPPL. 20 (1-24).

ISSN: 0730-2312 CODEN: JCEBD5
COUNTRY: United Sta
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 016 Cancer
017 Public Health, Social Medicine and Epidemiology
029 Clinical Biochemistry
052 Toxicology
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB This overview of the potential mechanisms of chemopreventive activity will provide the conceptual groundwork for chemopreventive drug discovery, leading to structure-activity and mechanistic studies that identify and evaluate new agents. Possible mechanisms of chemopreventive activity with examples of promising agents include carcinogen blocking activities such as inhibition of carcinogen uptake (calcium), inhibition of formation or activation of carcinogen (arylalkyl isothiocyanates, DHEA, NSAIDs, polyphenols), deactivation or detoxification of carcinogen (oltipraz, other GSH-enhancing agents), preventing carcinogen binding to DNA (oltipraz, polyphenols), and enhancing the level or fidelity of DNA repair (NAC, protease ***inhibitors***). Chemopreventive antioxidant activities include scavenging reactive electrophiles (GSH-enhancing agents), scavenging oxygen radicals (polyphenols, vitamin E), and inhibiting arachidonic acid metabolism (glycyrrhetinic acid, NAC, NSAIDs, polyphenols, tamoxifen). Antiproliferation/antiprogression activities include modulation of signal transduction (glycyrrhetinic acid, NSAIDs, polyphenols, retinoids, tamoxifen), modulation of hormonal and growth factor activity (NSAIDs, retinoids, tamoxifen), inhibition of aberrant oncogene activity (genistein, NSAIDs, monoterpenes), inhibition of polyamine metabolism (DFMO, retinoids, tamoxifen), induction of terminal differentiation (calcium, retinoids, vitamin D3), restoration of immune response (NSAIDs, selenium, vitamin E), enhancing intercellular communication (carotenoids, retinoids), restoration of ***tumor*** suppressor function, induction of programmed cell death (apoptosis) (***butyric*** ***acid*** , genistein, retinoids, tamoxifen), correction of ***DNA*** ***methylation*** imbalances (folic acid), inhibition of angiogenesis (genistein, retinoids, tamoxifen), inhibition of basement membrane degradation (protease ***inhibitors***), and activation of antimetastasis genes. A systematic drug development program for chemopreventive agents is only possible with continuing research into mechanisms of action and thoughtful application of the mechanisms to new drug design and discovery. One approach is to construct pharmacological activity profiles for promising agents. These profiles are compared among the promising agents and with untested compounds to identify similarities. Classical structure-activity studies are used to find optimal agents (high efficacy with low toxicity) based on good lead agents. Studies evaluating tissue-specific and pharmacokinetic parameters are very important. A final approach is design of mechanism-based assays and identification of mechanism-based intermediate biomarkers for evaluation of chemopreventive efficacy.

L15 ANSWER 21 OF 23 SCISEARCH COPYRIGHT 2002 ISI (R)
ACCESSION NUMBER: 2002:849157 SCISEARCH
THE GENUINE ARTICLE: 602RW
TITLE: Demethylation of a hypermethylated P15/INK4B gene in patients with myelodysplastic syndrome by 5-Aza-2 '-deoxycytidine (decitabine) treatment
AUTHOR: Daskalakis M; Nguyen T T; Nguyen C; Guldberg P; Kohler G; Wijermans P; Jones P A; Lubbert M (Reprint)
CORPORATE SOURCE: Univ Freiburg, Med Ctr, Dept Hematol Oncol, Hugstetter Str 55, D-79106 Freiburg, Germany (Reprint); Univ Freiburg, Med Ctr, Dept Hematol, D-79106 Freiburg, Germany; Leyenburg Hosp, Dept Hematol, The Hague, Netherlands; Danish Canc Soc, Inst Canc Biol, Copenhagen, Denmark; Univ Freiburg, Dept Pathol, D-7800 Freiburg, Germany; Univ Hosp, Dept Pathol, Munster, Germany; Univ So Calif, Norris Canc Ctr, Los Angeles, CA USA
COUNTRY OF AUTHOR: Germany; Netherlands; Denmark; USA
SOURCE: BLOOD, (15 OCT 2002) Vol. 100, No. 8, pp. 2957-2964. Publisher: AMER SOC HEMATOLOGY, 1900 M STREET. NW SUITE 200, WASHINGTON, DC 20036 USA.

ISSN: 0006-4971.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 51

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB p16 and p15,2 inhibitors of cyclin-dependent kinases, are frequently hypermethylated in hematologic neoplasias. Decitabine, or 5-Aza-2'-deoxycytidine, reverts hypermethylation of these genes in vitro, and low-dose decitabine treatment improves cytopenias and blast excess in similar to50% of patients with high-risk myelodysplastic syndrome (MDS). We examined p15 and p16 methylation status in bone marrow mononuclear cells from patients with high-risk MDS during treatment with decitabine, using a methylation-sensitive primer extension assay (Ms-SNuPE) to quantitate methylation, and denaturing gradient gel electrophoresis (DGGE) and bisulfite-DNA sequencing to distinguish individually methylated alleles. p15 expression was serially examined in bone marrow biopsies by immunohistochemistry. Hypermethylation in the 5' p15 gene region was detected in 15 of 23 patients (65%), whereas the 5' p16 region was unmethylated in all patients. Among 12 patients with hypermethylation sequentially analyzed after at least one course of decitabine treatment, a decrease in p 15 methylation occurred in 9 and was associated with clinical response. DGGE and sequence analyses were indicative of hypomethylation induction at individual alleles. Immunohistochemical staining for p15 protein in bone marrow biopsies from 8 patients with p15 hypermethylation revealed low or absent expression in 4 patients, which was induced to normal levels during decitabine treatment. In conclusion, frequent, selective p15 hypermethylation was reversed in responding MDS patients following treatment with a methylation inhibitor. The emergence of partially demethylated epigenotypes and re-establishment of normal p15 protein expression following the initial decitabine courses implicate pharmacologic demethylation as a possible mechanism resulting in hematologic response in MDS.

L15 ANSWER 22 OF 23 SCISEARCH COPYRIGHT 2002 ISI (R)
ACCESSION NUMBER: 2002:802579 SCISEARCH
THE GENUINE ARTICLE: 596KG
TITLE: Epigenetics wins over genetics: induction of differentiation in tumor cells
AUTHOR: Lotem J; Sachs L (Reprint)
CORPORATE SOURCE: Weizmann Inst Sci, Dept Mol Genet, POB 26, IL-76100 Rehovot, Israel (Reprint); Weizmann Inst Sci, Dept Mol Genet, IL-76100 Rehovot, Israel
COUNTRY OF AUTHOR: Israel
SOURCE: SEMINARS IN CANCER BIOLOGY, (OCT 2002) Vol. 12, No. 5, pp. 339-346.
Publisher: ACADEMIC PRESS LTD ELSEVIER SCIENCE LTD, 24-28 OVAL RD, LONDON NW1 7DX, ENGLAND.
ISSN: 1044-579X.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 96

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Malignant cells are genetically abnormal, but can the malignant phenotype revert to a non-malignant phenotype without correcting these genetic abnormalities? It has been found that this reversion can be achieved by reprogramming tumor cells by epigenetic changes induced by differentiation. The epigenetic suppression of malignancy by inducing differentiation bypasses the genetic abnormalities in tumor cells. Studies with myeloid leukemic cells have shown that some leukemic cells can be induced to differentiate by cytokines that control normal hematopoiesis, and that myeloid leukemic cells resistant to normal cytokines can be induced to differentiate by compounds that use alternative differentiation pathways. The epigenetic reprogramming of tumor cells by inducing differentiation has also been found with other types of tumors and can be used for tumor therapy. By this reversion of the malignant to non-malignant phenotype, epigenetics wins over genetics.

L15 ANSWER 23 OF 23 SCISEARCH COPYRIGHT 2002 ISI (R)
ACCESSION NUMBER: 2001:298593 SCISEARCH
THE GENUINE ARTICLE: 416LG
TITLE: The role of DNA methyltransferase 1 in growth control
AUTHOR: Szyf M (Reprint)

CORPORATE SOURCE: McGill Univ, Dept Pharmacol & Therapeut, 3655 Sir William Osler Promenade, Room 1309, Montreal, PQ H3G Y6, Canada (Reprint); McGill Univ, Dept Pharmacol & Therapeut, Montreal, PQ H3G 1Y6, Canada
COUNTRY OF AUTHOR: Canada
SOURCE: FRONTIERS IN BIOSCIENCE, (APR 2001) Vol. 6, pp. D599-D609. Publisher: FRONTIERS IN BIOSCIENCE INC, C/O NORTH SHORE UNIV HOSPITAL, BIOMEDICAL RESEARCH CENTER, 350 COMMUNITY DR, MANHASSET, NY 11030 USA. ISSN: 1093-9946.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 73

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Vertebrate DNA contains in addition to the four bases comprising the genetic information a modified base, 5-methyl cytosine that plays an important role in the epigenome. The methylated bases form a pattern of methylation that is cell specific and is faithfully inherited during cell division. The enzyme DNA methyltransferase 1 DNMT1 is responsible for copying the DNA methylation pattern but other de novo methyltransferase as well as demethylases might also be involved. Multiple mechanisms are in place to ensure the coordinate inheritance of the DNA methylation pattern with DNA replication. There is a bilateral relationship between the cell cycle and DNMT1. The expression of DNMT1 is tightly regulated with the cell cycle while the expression of DNMT1 can affect the cell cycle. DNMT1 protein might regulate cell cycle events by mechanisms that are independent of its DNA methylation activity through its multiple protein-protein interactions. The unique position of DNMT1 in the cell cycle is consistent with the hypothesis that it plays an important role in cancer.

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(FILE 'HOME' ENTERED AT 19:31:41 ON 21 NOV 2002)

FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH, AGRICOLA' ENTERED AT 19:32:09 ON 21 NOV 2002

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L1     5184193 S CANCER OR CARCINOMA OR SARCOMA OR TUMOR OR MALIGNANT OR LEUKE
L2        1777 S (DNA METHYLATION) (P) INHIBITOR
L3       32691 S CYTIDINE OR DECITABINE
L4       34371 S L2 OR L3
L5        3671 S (HISTONE DEACETYLASE) (P) INHIBITOR
L6       16304 S (HYDROXAMIC ACID) OR (TRICHOSTATIN A) OR OXAMFLATIN OR PYROXA
L7        4070 S (TRAPOXIN A) OR APICIDIN OR DEPSIPEPTIDE OR FR901228
L8       27241 S BENZAMIDE OR MS-27-275
L9      105163 S BUTYRATE OR (BUTYRIC ACID) OR PHENYLUTYRATE OR (ARGININE BUTY
L10     152314 S L5 OR L6 OR L7 OR L8 OR L9
L11        155 S L1 (P) L4 (P) L10
L12         95 S L11 (P) TREAT?
L13         27 DUPLICATE REMOVE L12 (68 DUPLICATES REMOVED)
L14         50 DUPLICATE REMOVE L11 (105 DUPLICATES REMOVED)
L15         23 S L14 NOT L13
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